

REVERSE HYDROXAMATE INHIBITORS OF MATRIX METALLOPROTEINASES

Cross Reference to Related Applications

This application is a continuation-in-part of U.S. Patent Application Ser. No. 09/129,360, filed August 5, 1998, pending.

Technical Field

This invention relates to compounds having activity to inhibit matrix metalloproteinases, to pharmaceutical compositions comprising these compounds and to a medical method of treatment. More particularly, this invention concerns reverse hydroxamate-containing compounds which inhibit matrix metalloproteinases, pharmaceutical compositions comprising these compounds and a method of inhibiting matrix metalloproteinases.

Background of the Invention

The matrix metalloproteinases (MMP's) are a class of extracellular enzymes including collagenase, stromelysin and gelatinase which are believed to be involved in the tissue destruction which accompanies a large number of disease states varying from arthritis to cancer.

Typical connective tissue cells are embedded within an extracellular matrix of high molecular weight proteins and glycoproteins. In healthy tissue, there is a continual and delicately-balanced series of processes which include cell division, matrix synthesis and matrix degradation. In certain pathological conditions, an imbalance of these three processes can lead to improper tissue restructuring. In arthritis, for example, joint mobility can be lost when there is improper remodelling of load-bearing joint cartilage. With cancer, lack of coordination of cell division and the two processes of matrix synthesis and degradation may lead to conversion of transformed cells to invasive phenotypes in which increased matrix turnover permits tumor cells to penetrate basement membranes surrounding capillaries which, in turn, may lead to subsequent metastasis.

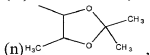
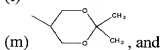
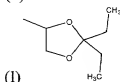
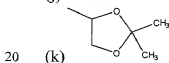
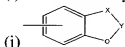
There has been heightened interest in discovering therapeutic agents which bind to and inhibit MMP's. The discovery of new therapeutic agents possessing this activity will lead to new drugs having a novel mechanism of action for combating disease states involving tissue degenerative processes including, for example, rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, corneal, epidermal or gastric ulceration, and tumor growth and metastasis or invasion.

Summary of the Invention

- (b) alkyl of one to six carbon atoms,
 (15) (heterocycle)oxyalkyl, wherein the alkylene group is of one to six carbon atoms,
 (16) -(alkylene)-S(O)_p-heterocycle, wherein the alkylene group is of one to six carbon atoms,
 5 (17) -(alkylene)-heterocycle, wherein the alkylene group is of one to six carbon atoms,
 (18) -(alkylene)-NR₆R₇, wherein the alkylene group is of one to six carbon atoms,
 (19) -heterocycle, and
 (20) -cycloalkyl,

wherein for (15)-(17) and (19), the heterocycle is selected from the group consisting of

- 10 (a) pyridyl,
 (b) pyrazinyl,
 (c) pyridazinyl,
 (d) furyl,
 (e) thienyl,
 15 (f) isoxazolyl,
 (g) oxazolyl,
 (h) thiazolyl,
 (i) isothiazolyl,

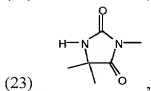
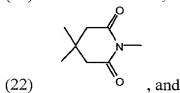
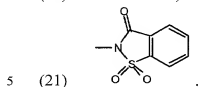
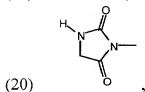
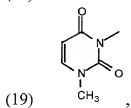
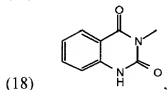
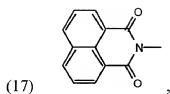


- wherein for (10)-(17) and (19), the phenyl, the phenyl parts of phenylalkoxyalkyl,
 25 phenylalkyl, -(alkylene)-N(R₅)SO₂-phenyl, phenoxyalkyl, and -(alkylene)-S(O)_p-phenyl,
 and the heterocycle, the heterocycle parts of (heterocycle)oxyalkyl, -(alkylene)-heterocycle
 and -(alkylene)-S(O)_p-heterocycle are optionally substituted with one, two, or three
 substituents independently selected from the group consisting of
 (a) alkyl of one to six carbon atoms,

- (b) alkoxy of one to six carbon atoms,
- (c) alkoxyalkyl, wherein the alkyl group and the alkylene group are independently of one to six carbon atoms,
- (d) halo,
- 5 (e) haloalkyl of one to six carbon atoms,
- (f) hydroxy,
- (g) hydroxyalkyl of one to six carbon atoms,
- (h) -(alkylene)-heterocycle, wherein the alkylene group is of one to six carbon atoms,
- (i) -(alkylene)-phenyl, wherein the alkylene group is of one to six carbon atoms,
- 10 (j) -N(R₅)SO₂-alkyl, wherein the alkyl group is of one to six carbon atoms,
- (k) phenyl, wherein the phenyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
 - (i) cyano,
 - (ii) nitro, and
 - 15 (iii) halo,
- (l) -C(O)OR₅, and
- (m) -C(O)NR_xR_y, wherein R_x and R_y are independently selected from the group consisting of
 - (i) alkyl of one to six carbon atoms,
 - 20 (ii) phenyl, and
 - (iii) phenylalkyl, wherein the alkyl group is of one to six carbon atoms, wherein for (ii) and (iii), the phenyl and the phenyl part of phenylalkyl are optionally substituted with substituents independently selected from the group consisting of halo and alkoxy of one to six carbon atoms, and
- 25 wherein for (18), R₆ and R₇ are independently selected from the group consisting of
 - (a) hydrogen,
 - (b) alkyl of one to six carbon atoms,
 - (c) cycloalkyl of three to eight carbon atoms,
 - (d) cycloalkylalkyl, wherein the cycloalkyl group is of three to eight carbon
 - 30 atoms, and the alkylene group is of one to ten carbon atoms,
 - (e) alkanoyl of one to ten carbon atoms,
 - (f) phenyl, and
 - (g) phenylalkyl, wherein the alkylene group is of three to ten carbon atoms, wherein for (f) and (g), the phenyl and the phenyl part of phenylalkyl are
 - 35 optionally substituted with one or two substituents independently selected from the group consisting of
 - (i) alkyl of one to six carbon atoms,

- (ii) alkoxy of one to six carbon atoms,
 (iii) perfluoroalkyl of one to six carbon atoms,
 (iv) halo,
 (v) haloalkyl of one to six carbon atoms, and
 5 (vi) alkanoyl of one to six carbon atoms, or
 R₆ and R₇, taken together with the nitrogen atom to which they are attached, define a group selected from the group consisting of
- (1) morpholinyl,
 (2) thiomorpholinyl,
 10 (3) thiomorpholinyl sulfone,
 (4) pyrrolidinyl,
 (5) piperazinyl,
 (6) piperidinyl,
 (7) succinimidyl,
 15 (8) maleimidyl,
 (9) glutarimidyl,
 (10) phthalimidyl,
 (11) naphthalimidyl,





wherein for (1)-(23), the groups defined by R₆ and R₇, together with the nitrogen atom to which they are attached, are optionally substituted with one or two substituents

10 independently selected from the group consisting of

- (a) halo,
- (b) alkyl of one to six carbon atoms,
- (c) alkoxy, wherein the alkyl part of the alkoxy is of one to six carbon atoms,
- (d) phenoxy,
- 15 (e) phenylalkyl, wherein the alkyl group is of one to six carbon atoms, and
- (f) benzyloxy; or

R₁ and **R₂**, taken together with the carbon atom to which they are attached form a ring selected from the group consisting of

- (1) spiroalkyl of three to eight carbon atoms and
- (2) tetrahydropyranyl; or

5

R₃ and **R₄**, taken together with the carbon atom to which they are attached, form a spiroalkyl group of three to eight carbon atoms; or

R₁ and **R₃** taken together with the carbon atoms to which they are attached are a 5, 6, or 7-membered carbocyclic ring;

10

X is selected from the group consisting of

- (1) -O-,
- (2) -NR₃SO₂-,
- (3) -S(O)_p-, and
- (4) -C(O)-,

15

wherein each group is drawn with its left-hand end being the end which attaches to the alkylene group and its right-hand end being the end which attaches to **Ar₁**;

20

Ar₁ is phenyl which is optionally substituted with one or two substituents independently selected from the group consisting of

- (a) alkyl of one to six carbon atoms,
- (b) perfluoroalkyl of one to six carbon atoms,
- (c) halo,
- (d) haloalkyl of one to six carbon atoms,
- (e) alkoxy of one to six carbon atoms,
- (f) hydroxy,
- (g) hydroxyalkyl of one to six carbon atoms,
- (h) alkoxyalkyl, wherein the alkyl and alkylene groups are independently of one to six carbon atoms, and
- (i) nitro;

25

30

Y is selected from the group consisting of

- (1) a covalent bond,
- (2) -O-,
- (3) alkylene of two to four carbon atoms,

35

- 09905242-071601
- (4) piperidineneyl,
 (5) alkenylene of two carbon atoms,
 (6) alkynylene of two carbon atoms,
 (7) -S(O)_p-, and
 5 (8) -C(O)-; and

Ar₂ is an aryl group selected from the group consisting of

- (1) phenyl,
 (2) pyridyl,
 10 (3) pyrazinyl,
 (4) pyridazinyl,
 (5) furyl,
 (6) thienyl,
 (7) isoxazolyl,
 15 (8) oxazolyl,
 (9) thiazolyl, and
 (10) isothiazolyl,

wherein the aryl group is optionally substituted with one, two, or three substituents independently selected from the group consisting of

- 20 (a) alkyl of one to six carbon atoms,
 (b) alkoxy of one to six carbon atoms,
 (c) alkoxy of one to six carbon atoms substituted with alkoxy of one to six carbon atoms,
 (d) -alkyl-CO₂R₅,
 25 (e) -alkyl-NR_xR_y,
 (f) alkoxyalkyl, wherein the alkyl group is of one to six carbon atoms, and the alkylene group is of one to six carbon atoms,
 (g) cyano,
 (h) cyanoalkyl of one to six carbon atoms,
 30 (i) halo,
 (j) haloalkyl of one to six carbon atoms,
 (k) hydroxy,
 (l) hydroxyalkyl of one to six carbon atoms,
 (m) hydroxyalkyl, wherein the alkyl group is of one to six carbon atoms,
 35 (n) thioalkoxy of one to six carbon atoms,
 (o) thioalkoxyalkyl, wherein the alkyl group is of one to six carbon

atoms, and the alkylene group is of one to six carbon atoms,

(p) phenylalkoxy, wherein the alkylene group is of one to six carbon atoms,

(q) phenoxy,

5 (r) phenoxyalkyl, wherein the alkylene group is of one to six carbon atoms,

(s) (heterocycle)oxy,

(t) (heterocycle)oxyalkyl, wherein the alkylene group is of one to six carbon atoms,

(u) perfluoroalkyl of one to six carbon atoms,

10 (v) perfluoroalkoxy, wherein the perfluoroalkyl part is of one to six carbon atoms,

(w) sulfinylalkyl, wherein the alkyl part is of one to six carbon atoms,

(x) sulfonylalkyl, wherein the alkyl part is of one to six carbon atoms,



(y) $\begin{array}{c} \text{---X} \\ | \\ \text{---O---Y} \end{array}$, wherein X is selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}_2\text{O}-$

15 and $-\text{O}-$, and Y is selected from the group consisting of $-\text{C}(\text{O})-$ and $-(\text{C}(\text{R}''))_2$, v -

where R" is hydrogen or alkyl of one to four carbon atoms, and v is 1-3,

(z) $-\text{N}(\text{R}_5)\text{SO}_2\text{R}_5$, wherein R_5 is defined previously and R_5' is selected from the group consisting of

(i) hydrogen and

20 (ii) alkyl of one to six carbon atoms, and

(aa) $-\text{SO}_2\text{N}(\text{R}_5)(\text{R}_5')$,

wherein for (s) and (t), the heterocycle part of (heterocycle)oxy, and

(heterocycle)oxyalkyl are selected from the group consisting of

(i) pyridyl,

25 (ii) pyrazinyl,

(iii) pyridazinyl,

(iv) furyl,

(v) thienyl,

(vi) isoxazolyl,

30 (vii) oxazolyl,

(viii) thiazolyl, and

(ix) isothiazolyl, and

wherein for (s) and (t), the heterocycle part of (heterocycle)oxy and

(heterocycle)oxyalkyl are optionally substituted with one or two substituents independently selected

35

from the group consisting of

- (i) alkyl of one to six carbon atoms,
- (ii) alkoxy of one to six carbon atoms,
- (iii) perfluoroalkyl of one to six carbon atoms,
- (iv) halo,
- (v) cyano,
- (vi) cyanoalkyl, wherein the alkyl is of one to six carbon atoms,
- (vii) haloalkyl of one to six carbon atoms, and
- (viii) alkanoyl of one to six carbon atoms, and

wherein for (q) and (r), the phenyl part of phenoxy and phenoxyalkyl are optionally substituted with one or two substituents independently selected from the group consisting of

- (i) alkyl of one to six carbon atoms,
- (ii) alkoxy of one to six carbon atoms,
- (iii) perfluoroalkyl of one to six carbon atoms,
- (iv) halo,
- (v) cyano,
- (vi) cyanoalkyl, wherein the alkyl is of one to six carbon atoms,
- (vii) haloalkyl of one to six carbon atoms, and
- (viii) alkanoyl of one to six carbon atoms.

In another embodiment, the present invention provides pharmaceutical compositions which comprise a therapeutically effective amount of compound of formula I in combination with a pharmaceutically acceptable carrier.

In yet another embodiment, the present invention provides a method of inhibiting matrix metalloproteinases in a host mammal in need of such treatment comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I.

Detailed Description of the Invention

Definition of Terms

As used throughout this specification and the appended claims, the following terms have the meanings specified:

The term "alkyl," as used herein, represents a monovalent group derived from a straight or branched chain saturated hydrocarbon by the removal of a single hydrogen atom and is exemplified by methyl, ethyl, n- and iso-propyl, n-, sec-, iso- and tert-butyl, neopentyl, and the like. The alkyl groups of this invention can be optionally substituted.

09905242.071604
1997-07-24 22:50:00

The term "alkanoyl," as used herein, represents an alkyl group, as defined above, attached to the parent molecular group through a carbonyl group and is exemplified by formyl, acetyl, propionyl, butanoyl, and the like. The alkanoyl groups of this invention can be optionally substituted.

5 The term "alkenyl," as used herein, represents monovalent straight or branched chain groups containing a carbon-carbon double bond derived from an alkene by the removal of one hydrogen atom and is exemplified by ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. The alkenyl groups of this invention can be optionally substituted.

10 The term "alkoxy," as used herein, represents an alkyl group attached to the parent molecular group through an oxygen atom. The alkyl part of the alkoxy group can be substituted with additional alkoxy groups. Alkoxy groups are exemplified by methoxy, isopropoxy, tert-butoxy, 2-methoxyethoxy, and the like. The alkoxy groups of this invention can be optionally substituted.

15 The term "alkoxyalkyl" as used herein, represents an alkyl group to which is attached an alkoxy group. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonyl," as used herein, represents an ester group, i.e. an alkoxy group attached to the parent molecular group through a carbonyl group, and is exemplified by methoxycarbonyl, ethoxycarbonyl, and the like. The alkoxycarbonyl groups of this invention can be optionally substituted.

20 The term "alkoxycarbonylalkyl," as used herein, represents an alkyl group, as defined above, substituted by a alkoxycarbonyl group. The alkoxycarbonylalkyl groups of this invention can be optionally substituted.

25 The term "alkylene," as used herein, represents a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms and is exemplified by methylene, ethylene, isopropylene, and the like. The alkylene groups of this invention can be optionally substituted.

The term "alkynyl," as used herein, represents monovalent straight or
30 branched chain groups of two to six carbon atoms containing a carbon-carbon triple bond derived from an alkyne by the removal of one hydrogen atom and is exemplified by ethynyl, 1-propynyl, and the like. The alkynyl groups of this invention can be optionally substituted.

The term "benzyloxy," as used herein, represents phenyl-(CH₂)-O-. The
35 benzyloxy groups of this invention can be optionally substituted.

The term "cyano," as used herein, represents a -CN group.

The term "cyanoalkyl," as used herein, represents a cyano group attached to the parent molecular moiety through an alkyl group. The cyanoalkyl groups of this invention can be optionally substituted.

The term "cycloalkyl," as used herein represents a monovalent saturated cyclic hydrocarbon group and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl, and the like. The cycloalkyl groups of this invention can be optionally substituted.

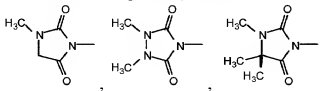
The term "cycloalkylalkyl," as used herein, represents a cycloalkyl group attached to the parent molecular group through an alkylene group. The cycloalkylalkyl groups of this invention can be optionally substituted.

The term "halo," as used herein, represents F, Cl, Br, and I.

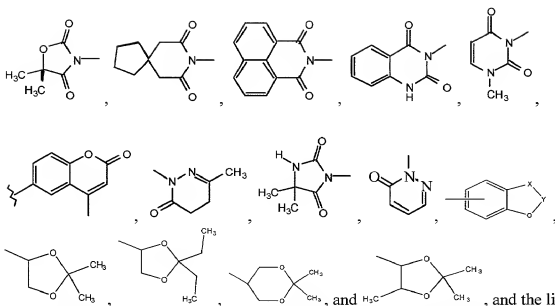
The term "haloalkyl," as used herein, represents an alkyl group substituted by one, two, three or four halogen atoms and is exemplified by chloromethyl, bromoethyl, chlorodifluoromethyl, and the like. The haloalkyl groups of this invention can be optionally substituted.

The term "heterocycle," as used herein, represents a five-, six- or seven-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. The five-membered ring has zero to two double bonds and the six- and seven-membered rings have zero to three double bonds.

Heterocycles include indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, benzothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolynyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiomorpholino sulfone, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyrimidyl, tetrahydrofuranlyl, dihydrofuranlyl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyranyl, dihydropyranyl, dithiazolyl, benzofuranlyl, benzothienyl, succinimidyl, maleimidyl, glutarimidyl, phthalimidyl, naphthalimidyl, and the like. The heterocycle groups of this invention can be optionally substituted.



Heterocycles also include



wherein X is selected from $-\text{CH}_2-$, $-\text{CH}_2\text{O}-$ and $-\text{O}-$, and Y is selected from $-\text{C}(\text{O})-$ and $-(\text{C}(\text{R}'')_2)_v-$, where R'' is hydrogen or alkyl of one to four carbons, and v is 1-3.

The term "(heterocycle)oxy," as used herein, represents a heterocycle group attached to the parent molecular moiety through oxygen. The (heterocycle)oxy groups of this invention can be optionally substituted.

The term "(heterocycle)oxyalkyl," as used herein, represents a (heterocycle)oxy group attached to the parent molecular group through an alkyl group. The (heterocycle)oxyalkyl groups of this invention can be optionally substituted.

The term "hydroxy" as used herein, represents an -OH group.

The term "hydroxyalkyl," as used herein, represents an alkyl group, as defined above, substituted by one to three hydroxy groups, with the proviso that no more than one hydroxy group may be attached to a single carbon atom of the alkyl group and is exemplified by hydroxymethyl, dihydroxypropyl, and the like. The hydroxyalkyl groups of this invention can be optionally substituted.

The term "nitro," as used herein, refers to -NO₂.

The term "perfluoroalkyl," as used herein, represents an alkyl group, as defined herein, wherein each hydrogen radical bound to the alkyl group has been replaced by a fluoride radical. Perfluoroalkyl groups are exemplified by trifluoromethyl, pentafluoroethyl, and the like. The perfluoroalkyl groups of this invention can be optionally substituted.

The term "perfluoroalkoxy," as used herein, refers to a perfluoroalkyl group, as defined herein, attached to the parent molecular group through an oxygen atom. The perfluoroalkoxy groups of this invention can be optionally substituted.

0905242.071601

The term "pharmaceutically acceptable salt," as use herein, represents those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio.

5 Pharmaceutically acceptable salts are well known in the art. For example, S. M Berge, et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66:1-19. The salts can be prepared in situ during the final isolation and purification of the compounds of the invention or separately by reacting the free base group with a suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, 10 ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 15 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium and the like, as well as nontoxic ammonium, quaternary 20 ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like.

25 The term "phenoxy," as used herein, represents a phenyl group attached to the parent molecular group through an oxygen atom. The phenoxy groups of this invention can be optionally substituted.

The term "phenoxyalkyl," as used herein, represents a phenoxy group attached to the parent molecular group through an alkyl group. The phenoxyalkyl groups of this invention can be optionally substituted.

30 The term "phenyl," as used herein, represents a 6-membered, monocyclic, aromatic carbocyclic ring. The phenyl groups of this invention can be optionally substituted.

The term "phenylalkyl," as used herein, represents an phenyl group attached to the parent molecular group through an alkylene group and is exemplified by benzyl, phenethyl, and the like. The phenylalkyl groups of this invention can be optionally substituted.

35 The term "phenylalkoxy," as used herein, represents a phenyl group attached to the parent molecular group through an alkoxy group. The phenylalkoxy groups of this invention can be optionally substituted.

1005242.071601

The term "phenylalkoxyalkyl" as used herein, represents a phenylalkoxy group, as defined above, attached to the parent molecular group through an alkyl group. The phenylalkoxyalkyl groups of this invention can be optionally substituted.

The term "piperidineneyl," as used herein, represents a divalent group derived from piperidine by the removal of two hydrogen atoms. The piperidineneyl groups of this invention can be optionally substituted.

The term "prodrug," as used herein, represents compounds which are rapidly transformed in vivo to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference. Prodrugs of the compounds of the present invention are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention.

The term "spiroalkyl," as used herein, represents an alkylene diradical, both ends of which are bonded to the same carbon atom of the parent group to form a spirocyclic group. The spiroalkyl groups of this invention can be optionally substituted.

The term "sulfinyl," as used herein, refers to an -S(O)- group.

The term "sulfinylalkyl," as used herein, refers to an alkyl group, as defined herein, attached to the parent molecular group through a sulfinyl group.

The term "sulfonyl," as used herein, refers to an -SO₂- group.

The term "sulfonylalkyl," as used herein, refers to an alkyl group, as defined herein, attached to the parent molecular group through a sulfonyl group. The sulfonylalkyl groups of this invention can be optionally substituted.

The term "thioalkoxy," as used herein, represents an alkyl group attached to the parent molecular group through a sulfur atom. The thioalkoxy groups of this invention can be optionally substituted.

Compounds of the present invention may exist as stereoisomers, wherein asymmetric or chiral centers are present. These compounds are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. The present invention contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers are designated (\pm). Individual stereoisomers of compounds of the present invention may be prepared synthetically from commercially available

starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

Preferred Embodiments

Preferred compounds of the present invention have formula (I), wherein

R₁, R₃ and R₄ are H;

X is selected from the group consisting of

(1) -O-,

(2) -C(O)-,

(3) -S(O)_p-, wherein p is 2, and

(4) -NR₅SO₂-;

Ar₁ is phenyl;

Y is selected from the group consisting of a

(1) covalent bond and

(2) -O-; and

n is zero;

More preferred compounds of the present invention have formula (I), wherein

R₁, R₃ and R₄ are H;

X is -O- and -S(O)_p;

Ar₁ is phenyl;

Y is a covalent bond; and

n is zero.

Preferred compounds falling within the scope of formula (I) include but are not limited to:

([±])-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-phenoxyethyl]-N-hydroxyformamide;

([±])-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(phenylthio)ethyl]-N-hydroxyformamide;

([±])-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(2,3-dihydro-1,3-dioxo-1H-indol-2-yl)ethyl]-N-hydroxyformamide;

([±])-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-N-hydroxyformamide;

([±])-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-3-(3,4,4-trimethyl-

2,5-dioxoimidazolidin-1-yl)propyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[3'-(cyanomethyl)-[1,1'-biphenyl]-4-yl]oxy]methyl]pentyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-3-methylbutyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-methylbutyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]pentyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4-methylphenyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[2-[(4'-cyano-[1,1'-biphenyl]-4-yl]oxy]-1-(4-fluorophenyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4-fluorophenyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[2-[(4'-cyano-[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[4-[(2*E*-phenylethenyl)phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[4-(2-furanyl)phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-butoxy[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-fluoro[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-methoxy[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-methyl[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-butoxy[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[(4'-ethoxy[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4-(1,3-benzodioxol-5-yl)phenoxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-

1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-butoxy[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3-methoxy-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[4-(3-thienyl)phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 5 (±)-*N*-[1-[[[4'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-chloro-4'-fluoro[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 10 (±)-*N*-[1-[[[2'-methyl[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)ethyl]-*N*-hydroxyformamide;
 15 (±)-*N*-[1-[[4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[4-(4-phenyl-1-piperidinyl)phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 20 (±)-*N*-[1-[[4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[3'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-[methyl[(4-methylphenyl)sulfonyl]amino]ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-[4,4-dimethyl-2,5-dioxo-3-(3-pyridinyl)methyl]-1-imidazolidinyl]ethyl]-*N*-hydroxyformamide;
 25 (±)-*N*-[2-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]-1-methylpropyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[3'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 30 (±)-*N*-[1-[[[4'-(methylthio)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-4-[[[4-(trifluoromethyl)phenoxy]phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 (±)-*N*-[1-[[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
 35 (±)-*N*-[1-[[[4'-(methylsulfonyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-[[[3'-(cyanomethyl)-4'-methoxyl[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[3'-(cyanomethyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-3-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)propyl]-*N*-hydroxyformamide;
5 (\pm)-*N*-[1-[[[4'-butoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-3-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)propyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4'-(methylsulfonyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
10 (\pm)-*N*-[1-[[[3'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethyl-2,6-dioxo-1-piperidinyl)ethyl]-*N*-hydroxyformamide;
15 (\pm)-*N*-[1S-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1R-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3-ethyl-3-methyl-2,5-dioxo-1-pyrrolidinyl)ethyl]-*N*-hydroxyformamide;
20 *N*-[4-[4-[[[4-chlorophenoxy]phenyl)sulfonyl]methyl]tetrahydro-2H-pyran-4-yl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-[[[2-methoxycarbonyl]phenyl]thio]ethyl]-*N*-hydroxyformamide;
25 (\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-5-[(4-methyl-2-oxo-2H-1-benzopyran-6-yl)oxy]pentyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-4-[(4-methyl-2-oxo-2H-1-benzopyran-6-yl)oxy]butyl]-*N*-hydroxyformamide;
30 (\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-4-[(4-methyl-2-oxo-2H-1-benzopyran-7-yl)oxy]butyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-5-[(4-methyl-2-oxo-2H-1-benzopyran-7-yl)oxy]pentyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(5,5-dimethyl-2,4-dioxo-3-oxazolidinyl)ethyl]-*N*-hydroxyformamide;
35 (\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl)sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;

5 (\pm)-*N*-[1-[[[(4'-chloro[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-[[[(3'-cyanomethyl-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,5,5-trimethyl-2,4-dioxo-1-imidazolidinyl)propyl]-*N*-hydroxyformamide;

10 (\pm)-*N*-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-isopropylthioethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-[[[(3'-cyanomethyl-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3-ethyl-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;

15 (\pm)-*N*-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3-benzyl-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,5,5-trimethyl-2,4-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;

20 (\pm)-*N*-[1-[[[4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-[[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]methyl]ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-[[[4-(1,3-benzodioxol-5-yl)phenyl]sulfonyl]methyl]ethyl]-*N*-hydroxyformamide;

25 (\pm)-*N*-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-[[[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]propyl]-*N*-hydroxyformamide;

30 (\pm)-*N*-[1-[1,1-dimethyl-2-[(4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)sulfonyl]ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-(phenylmethoxy)methyl]-2-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)sulfonyl]ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-(hydroxymethyl)-2-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)sulfonyl]ethyl]-*N*-hydroxyformamide;

35 (\pm)-*N*-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]thio]ethyl]-*N*-hydroxyformamide;

- (\pm)-*N*-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[(2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[4'-butyl[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[(3-methyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
- N*-[4-[4-(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]methyl]tetrahydro-2H-pyran-4-yl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[4-butyl[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[4'-butyl[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[3'-(cyanomethyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[4-(2-thienyl)phenoxy]methyl]-2-[1-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[3-nitro[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[4'-methyl[1,1'-biphenyl]-4-yl]oxy]methyl]-2-[[3-(methylsulfonyl)-amino]phenyl]ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[3-(diethylamino)carbonyl]phenyl]methyl]-2-[(4'-methyl[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-[(4'-cyano[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(2-methoxyethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;

(\pm)-*N*-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[(4'-propoxy[1,1'-biphenyl]-4-yl)oxy]ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[(4'-
5 pentyloxy[1,1'-biphenyl]-4-yl)oxy]ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[3'-(cyanomethyl)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-3-(4,4-
dimethyl-2,5-dioxo-1-imidazolidinyl)propyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(3,4,4-
trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(3-methyl-2,5-dioxo-
10 1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[3'-(cyanomethyl)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(3,4,4-
trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4'-cyano[1,1''-biphenyl]-4-yl]oxy]methyl]-2-(1,6-dihydro-3-methyl-
6-oxo-1-pyridazinyl)ethyl]-*N*-hydroxyformamide;
15 (\pm)-*N*-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(4,4-dimethyl-2,5-
dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[[4-(4-fluorophenoxy)phenyl]sulfonyl]methyl]-2-(4,4-dimethyl-2,5-
dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-[1-[[4-(4-pyridinyl)phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-
20 imidazolidinyl)ethyl]-*N*-hydroxyformamide;
(*S*)-*N*-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(
trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
(*R*)-*N*-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(
trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
25 *N*-[1-[[[4'-(trifluoromethoxy)][1,1'-biphenyl]-4-yl]oxy]methyl]-3-(4,4-dimethyl-
2,5-dioxo-1-imidazolidinyl)propyl]-*N*-hydroxyformamide;
N-[1-[4-[(4-pyridinylthio)phenoxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-
imidazolidinyl)ethyl]-*N*-hydroxyformamide;
30 *N*-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-3-(4,4-dimethyl-2,5-dioxo-1-
imidazolidinyl)propyl]-*N*-hydroxyformamide;
N-[1-[[[4'-cyano[1,1''-biphenyl]-4-yl]oxy]methyl]-2-(1,6-dihydro-6-oxo-1-
pyridazinyl)ethyl]-*N*-hydroxyformamide;
N-[1-[[[4'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-
2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
35 *N*-[1-[[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(4,4-
dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;

N -[1-[4-[(4-pyridinyloxy)phenyl]sulfonyl]ethyl]- N -hydroxyformamide;
 N -[1-[[[(4-cyanophenoxy)phenyl]sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]- N -hydroxyformamide;
 N -[1-[[4-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]methyl]-3-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)propyl]- N -hydroxyformamide;
 N -[1-[[4-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]- N -hydroxyformamide;
 (\pm) - N -hydroxy- N -[1-(3-pyridinyl)-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-sulfonyl]ethyl]formamide; (\pm) - N -hydroxy- N -[1-(hydroxymethyl)-2-[[4-[(4-chlorophenoxy)phenyl]sulfonyl]-ethyl]formamide;
 (\pm) - N -hydroxy- N -[1-methyl-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]-ethyl]formamide;
 (\pm) - N -hydroxy- N -[1-(2-pyridinyl)-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-sulfonyl]ethyl]formamide;
 (\pm) - N -[1-[4-(4,4-dimethyl-2,6-dioxo-1-piperidinyl)methyl]-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]- N -hydroxyformamide;
 (\pm) - N -hydroxy- N -[3-hydroxy-1-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]-methyl]propyl]formamide;
 (\pm) - N -hydroxy- N -[1-(methoxymethyl)-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide;
 (\pm) - N -[1-(1,3-benzodioxol-5-yl)-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]-ethyl]- N -hydroxyformamide;
 (\pm) - N -hydroxy- N -[4-hydroxy-1-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]-methyl]butyl]formamide;
 (\pm) - N -hydroxy- N -[1-[4-(methoxymethoxy)phenyl]-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide;
 (\pm) - N -hydroxy- N -[1-(1-methyl-1H-pyrrol-2-yl)-2-[[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl]ethyl]formamide;
 (\pm) - N -hydroxy- N -[1-phenyl-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-ethyl]formamide;
 (\pm) - N -hydroxy- N -[1-(2-thienyl)-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-ethyl]formamide;
 (\pm) - N -[1-(2-furanyl)-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]- N -hydroxyformamide;
 (\pm) - N -[1-(5,5-dimethyl-2,4-dioxo-3-oxazolidinyl)-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]- N -hydroxyformamide;

(\pm)-*N*-hydroxy-*N*-[1-(methoxymethyl)-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]formamide;
(\pm)-*N*-hydroxy-*N*-[1-[(phenylmethoxy)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]formamide;
5 (\pm)-*N*-hydroxy-*N*-[1-(hydroxymethyl)-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]formamide;
(\pm)-*N*-hydroxy-*N*-[1-(hydroxymethyl)-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]formamide;
[S-(R*,S*)]-*N*-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]-*N*-hydroxyformamide;
10 [S-(R*,R*)]-*N*-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]-*N*-hydroxyformamide;
[S-(R*,R*)]-*N*-hydroxy-*N*-[(2,3-dihydroxy)-1-[[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]methyl]propyl]-*N*-hydroxyformamide;
15 (\pm)-*N*-[1-[(dimethylamino)methyl]-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]-*N*-hydroxyformamide;
[S-(R*,R*)]-*N*-[2-[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]-1-(2,2-dimethyl-1,3-dioxol-4-yl)ethyl]-*N*-hydroxyformamide;
20 (\pm)-*N*-[1-[(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide;
[R-(R*,R*)]-*N*-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]-*N*-hydroxyformamide;
[R-(S*,R*)]-*N*-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]-*N*-hydroxyformamide;
25 [S-(R*,R*)]-*N*-[1-(2,2-diethyl-1,3-dioxol-4-yl)-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-hydroxy-*N*-[1-(hydroxymethyl)-2-[[4'-(methylsulfonyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide;
30 (\pm)-*N*-[1-[[4-[(1,3-benzodioxol-5-yl)phenyl)sulfonyl]methyl]-2-hydroxyethyl]-*N*-hydroxyformamide;
(\pm)-*N*-hydroxy-*N*-[1-(hydroxymethyl)-2-[[4'-(methylthio)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide;
(\pm)-*N*-hydroxy-*N*-[1-(hydroxymethyl)-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide;
35

- (\pm)-*N*-hydroxy-*N*-[1-(hydroxymethyl)-2-[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]ethyl]formamide;
- (\pm)-*N*-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-hydroxy-*N*-[1-(hydroxymethyl)-2-[[[4-(methylsulfonyl)phenoxy]phenyl]sulfonyl]ethyl]formamide;
- (\pm)-*N*-[1-methyl-3-(4'-chloro[1,1'-biphenyl]-4-yl)-3-oxopropyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-(4-butylphenoxy)-phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[3-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)-1-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]methyl]propyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[4-[(4-chlorophenoxy)phenyl]sulfonyl]methyl]-3-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]propyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[2-[4-(4'-cyano[1,1'-biphenyl]-4-yl)oxy]cyclohexyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[2-[4-[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl)oxy]cyclohexyl]-*N*-hydroxyformamide;
- (\pm)-1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(3-methyl-6-oxo-1(6H)-pyridazinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-hydroxy-[1-[(6-oxo-1(6H)-pyridazinyl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]formamide;
- (\pm)-*N*-[1-[(1,6-dihydro-3-methyl-2,6-dioxo-1(6H)-pyrimidinyl)methyl]-2-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[(1,6-dihydro-3-methyl-2,6-dioxo-1(6H)-pyrimidinyl)methyl]-2-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-methyl-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]propyl]-*N*-hydroxyformamide;
- (\pm)-*N*-[1-[[4-[(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(1,6-dihydro-3-methyl-2,6-dioxo-1(6H)-pyrimidinyl)ethyl]-*N*-hydroxyformamide;
- (\pm)-*N*-hydroxy-*N*-[1-[(3-methyl-6-oxo-1(6H)-pyridazinyl)methyl]-2-[[4-[4-(trifluoro-methoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide;
- (\pm)-*N*-hydroxy-*N*-[1-(1-methyl-1H-indol-4-yl)-[2-[[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl]ethyl]formamide;

(\pm)-*N*-hydroxy-*N*-[1-(1-methyl-1*H*-indol-2-yl)-2-[[4-(4-(trifluoromethoxy)phenoxy)-phenyl]sulfonyl]ethyl]formamide;
(\pm)-*N*-[1-(4-chlorophenyl)-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide;
5 (\pm)-*N*-hydroxy-*N*-[2-[[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-1-(4-(trifluoro-methyl)phenyl]ethyl]formamide;
(\pm)-*N*-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-hydroxy-*N*-[1-[[4-(thienylthio)methyl]-2-[[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl]ethyl]formamide;
10 (\pm)-*N*-hydroxy-*N*-[1-[[[4-(methylphenyl)sulfonyl]methy lamino]methyl]-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide;
(\pm)-*N*-hydroxy-*N*-[[[2-(methoxyethoxy)methyl]-1-[[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl]ethyl]formamide;
15 (\pm)-*N*-[1-[(1,6-dihydro-3-methyl-2,6-dioxo-1(6*H*)-pyrimidinyl)methyl]-2-[[4-(phenoxyphenyl)sulfonyl]ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-hydroxy-*N*-[1-(4-hydroxyphenyl)-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide;
(\pm)-*N*-hydroxy-*N*-[1-(2,2-dimethyl-1,3-dioxan-5-yl)-2-[[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl]ethyl]formamide;
20 (\pm)-*N*-hydroxy-*N*-[3-hydroxy-2-(hydroxymethyl)-1-[[[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl]methyl]propyl]formamide;
(\pm)-*N*-hydroxy-*N*-[1-(hydroxymethyl)-2-[[[4-(chlorophenyl)thio]phenyl]sulfonyl]ethyl]formamide;
25 (\pm)-*N*-hydroxy-*N*-[1-(4-morpholinyl)methyl]-2-[[[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl]ethyl]formamide;
(\pm)-*N*-hydroxy-*N*-[4-hydroxy-[1-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-butyl]formamide;
(\pm)-*N*-[1-[(1*H*-isoindole-1,3(2*H*)-dione)methyl]-2-[[4-(4-chlorophenoxy)phenyl]-sulfonyl]ethyl]-*N*-hydroxyformamide;
30 (\pm)-*N*-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-(4-cyano-phenoxy)phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide;
(\pm)-*N*-hydroxy-*N*-[1-(2-pyridinyl)-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide;
35 (\pm)-*N*-[1-[[[4-(chlorophenoxy)phenyl]sulfonyl]methyl]-4-hydroxybutyl]-*N*-hydroxy-formamide;

([±])-*N*-[1-[[[(4-trifluoromethoxyphenoxy)phenyl]sulfonyl]methyl]-3-hydroxypropyl]-*N*-hydroxyformamide;
([±])-*N*-hydroxy-*N*-[1-[(4-trifluoromethoxyphenoxy)methyl]-2-[[4-(4-(trifluoromethoxy)phenoxy)phenyl]sulfonyl]ethyl]formamide;
5 [S-(R*,R*)]-*N*-hydroxy-*N*-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[4-[(4-phenyl-1-piperidinyl)phenyl]sulfonyl]ethyl]formamide;
([±])-*N*-hydroxy-*N*-[1-(4-trifluoromethoxyphenyl)-2-[[4-(4-(trifluoromethoxy)phenoxy)-phenyl]sulfonyl]ethyl]formamide;
10 [S-(R*,R*,R*)]-*N*-[1-(2,2,5-trimethyl-1,3-dioxol-4-yl)-2-[[4-(4-(trifluoromethoxy)-phenoxy)phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide;
([±])-*N*-hydroxy-*N*-[1-(2-trifluoromethylphenyl)-2-[[4-(4-(trifluoromethoxy)phenoxy)-phenyl]sulfonyl]ethyl]formamide;
([±])-*N*-hydroxy-*N*-[1-(4-fluorophenyl)-2-[[4-(4-(trifluoromethoxy)phenoxy)phenyl]sulfonyl]ethyl]formamide;
15 ([±])-*N*-hydroxy-*N*-[1-(cyclohexyl)-2-[[4-(4-(trifluoromethoxy)phenoxy)phenyl]sulfonyl]ethyl]formamide;
(-)-(S)-*N*-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide;
([±])-*N*-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-(4-bromophenoxy)phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide; and
20 ([±])-*N*-hydroxy-*N*-[1-[[[4-(4-(trifluorophenoxy)phenyl]sulfonyl]methyl]-2-(3,4,5-trimethoxyphenyl)ethyl]formamide.

Pharmaceutical Compositions

25 The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

30 The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally or topically (such as powders, ointments or drops), buccally or as an oral or nasal spray. The term "parenteral" administration, as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal,
35 subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents (such as aluminum monostearate and gelatin) which delay absorption.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microcapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is mixed with at least one

inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally or in delayed fashion.

Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds may also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters,

microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention. Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

Generally dosage levels of about 1 to about 50, more preferably of about 5 to about 20 mg, of active compound per kilogram of body weight per day when administered orally to a mammalian patient. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.

Determination of Stromelysin Inhibition

The efficacy of the compounds of this invention as matrix metalloproteinase inhibitors was determined by measuring the inhibition of stromelysin. The inhibition of stromelysin by the compounds of this invention was determined as follows: Recombinant truncated stromelysin (human sequence) produced in *E. coli* was prepared by expression and purification of the protein as described by Ye et al. (Biochemistry, 1992, 31, 11231-11235, which is incorporated herein by reference). The enzyme was assayed by its cleavage of the thiopeptide ester substrate Ac-Pro-Leu-Gly-[2-mercapto-4-methyl-pentanoyl]-Leu-Gly-OEt as described by Weingarten and Feder (Anal. Biochem., 1985, 147, 437-440 (1985), which is incorporated herein by reference) as a substrate of vertebrate collagenase. The reported conditions were modified to allow assays to be carried out in a microtiter plate. Upon hydrolysis of the thioester bond, the released thiol group reacted rapidly with 5,5'-dithio-bis(2-nitrobenzoic acid) (DTNB) to produce a yellow color which was measured by a microtiter plate reader set at 405 nm. The rates of cleavage of the substrate by stromelysin in the presence or absence of inhibitors were measured in a 30 minute assay at ambient temperature. Solutions of the compounds in DMSO were prepared, and these were diluted at various concentrations into the assay buffer (50 mM MES/NaOH pH 6.5 with 10 mM CaCl₂ and 0.2% Pluronic F-68), which was also used for dilution of the enzyme and substrate. The potency of the compounds [IC₅₀] was calculated from the inhibition/inhibitor concentration data. The compounds of this invention inhibited stromelysin as shown by the data for representative examples in Table 1.

Table 1

Example	IC ₅₀ (nM)
1	130
2	36
3	21
4	9.1
5	17
6	30
7	120
8	170
9	100
10	1,500
11	300

12	180
13	310
14	4,000
15	620

Preparation of Compounds of this Invention

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes which are merely illustrative of the methods by which the compounds of the invention may be prepared and are not intended to limit the scope of the invention as defined in the appended claims. Representative procedures are outlined in the following Schemes 1-5.

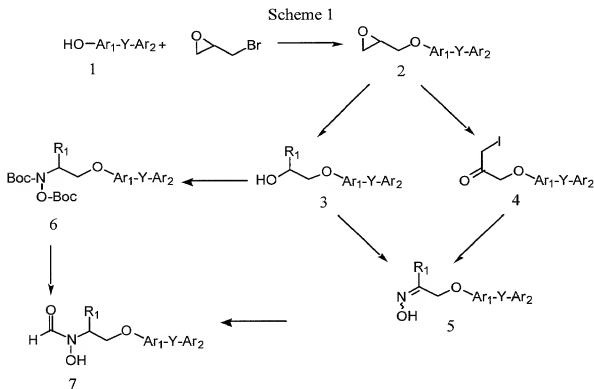
Abbreviations

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are: THF for tetrahydrofuran; DMF for N,N-dimethylformamide; rt for room temperature; TBDMSCl for *tert*-butyldimethylsilyl chloride; h for hour; decomp. for decomposition; sat. for saturated; LAH for lithiumaluminum chloride; min for minutes; aq. for aqueous; and *m*-CPBA for *meta*-chloroperbenzoic acid.

As shown in Scheme 1, deprotonation of the phenolic moiety of 1 with a base, preferably sodium or potassium hydride, and alkylation of the resulting anion with an excess, preferably a two to four-fold excess, of an electrophile, preferably epibromohydrin or epichlorohydrin, provided the alkylated epoxide 2. An excess of a second nucleophile, preferably a two to four-fold excess, was deprotonated with a base such as sodium or potassium hydride and condensed with 2 to provide alcohol 3 which was treated with bis-Boc-hydroxylamine under Mitsunobu conditions to provide the bis-Boc protected hydroxylamine 6. Removal of the Boc-protecting groups with acid, preferably HCl in dioxane or trifluoroacetic acid in methylene chloride, and neutralization of the amine salt with a base, preferably sodium bicarbonate, provided an exposed hydroxylamine moiety which was treated with a formylating agent, preferably formicacetyl anhydride, in solvents such as THF or dichloromethane to provide hydroxamic acid 7.

Alternatively, 2 was converted to the corresponding iodoketone 4 by a two-step procedure which comprised (a) treatment of the epoxide with triphenylphosphine and an iodinating agent, preferably iodine, in an inert solvent such as dichloromethane to provide the corresponding iodoalcohol followed by (b) oxidation to the corresponding iodoketone 4 with a mild oxidizing agent, preferably Dess-Martin periodinane (Dess, D. B.; Martin, J.

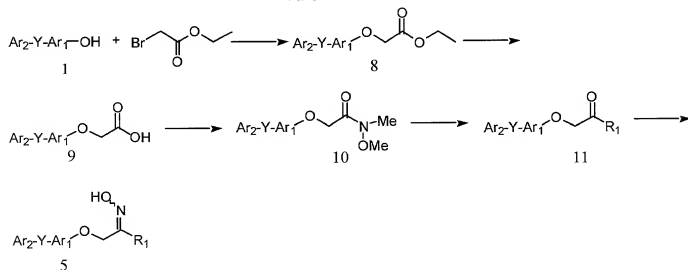
C., J. Am. Chem. Soc. 1991, 113, 7277-7287, which is incorporated herein by reference). Introduction of R_1 was accomplished by alkylation of the desired phenol or benzenethiol derivative with 4 in the presence of base, preferably potassium carbonate, in a polar solvent such as DMF. The resulting ketone was converted to the corresponding oxime 5 by treatment with hydroxylamine hydrochloride in a hydroxylic solvent, preferably ethanol, with a catalytic amount of base, preferably pyridine. When R_1 contained sulfur, the alcohol was oxidized to the corresponding ketone using Dess-Martin periodinane in an inert solvent such as dichloromethane then converted to 5 as described above. Treatment of 5 with a reducing agent, preferably borane-pyridine complex, in a hydroxylic solvent, preferably ethanol, and adding excess aqueous hydrochloric acid provided the corresponding hydroxylamine which was formylated as described above to provide 7. Depending on the nature of R_1 group, protection and subsequent deprotection of other reactive groups was required to successfully complete the described synthetic sequences. Commonly used protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is incorporated herein by reference.



Scheme 2 shows an alternate preparation of intermediate 5. Alkylation of 1 with ethyl bromoacetate was accomplished in the presence of base, preferably potassium carbonate, in a polar solvent, preferably DMF, to provide 8, which was subsequently

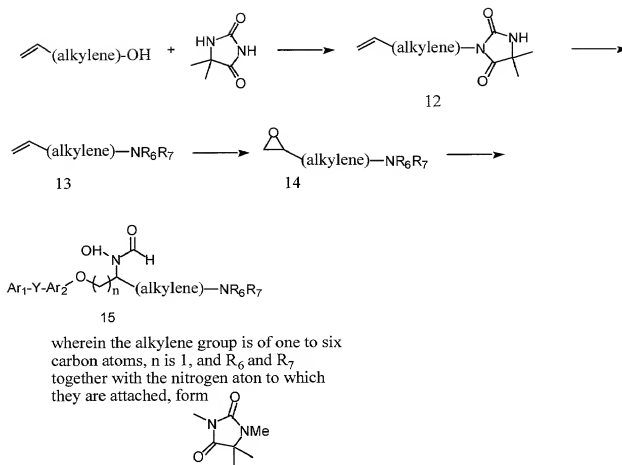
hydrolyzed to 9 by treatment with aqueous base, preferably lithium hydroxide in a solvent mixture, preferably water and dioxane. Amide 10 was prepared by coupling N,O-dimethylhydroxylamine hydrochloride to 9 with a coupling agent, preferably bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl). Treatment of 10 with R_1 -MgX, wherein X is Br or Cl, at reduced temperature, preferably -78 °C in an inert solvent, preferably THF, provided ketone 11, which was converted to 5, and finally to 7, as described in Scheme 1.

Scheme 2



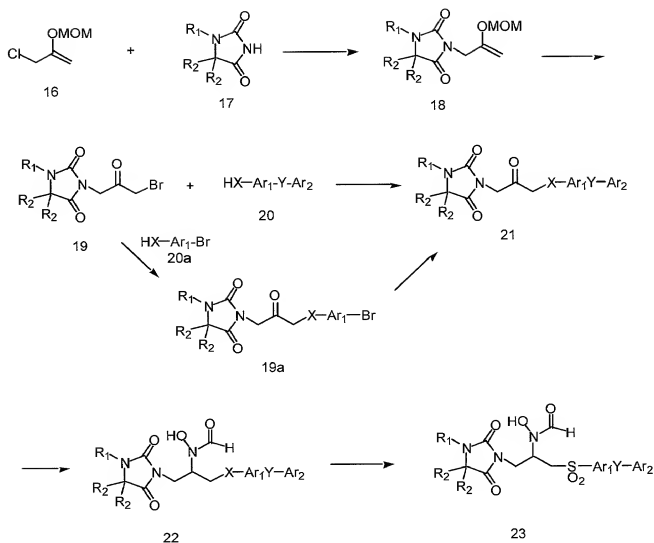
Scheme 3 shows the synthesis of compounds where the introduction of the phenolic and R_1 groups was reversed. This route intersects with the route described in Scheme 1 at epoxide 14, and the chemistry described in Scheme 1 may be utilized to convert 14 into the hydroxamic acid by employing $\text{HO-Ar}_1\text{-Y-Ar}_2$ in place of $R_1\text{-H}$. Heterocyclic derivatives of $R_1\text{-H}$, preferably those having appropriate pK_a 's, such as the hydantoin in this scheme, were condensed with the desired olefinic alcohol under Mitsunobu conditions to provide the corresponding N-alkenylheterocycle 12. Treatment of 12 with an alkylating agent, preferably methyl iodide, in the presence of base, preferably sodium hydride, provided N-methyl alkenylheterocycle 13, which was epoxidized with meta-chloroperoxybenzoic acid (MCPBA) in dichloromethane to provide 14. The reaction sequence described in Scheme 1 was then used to convert 14 to hydroxamic acid 5.

Scheme 3



Scheme 4 shows an alternate synthesis of the hydantoin substituted compounds 22 and 23. Alkylation of 16 with a substituted hydantoin 17 in the presence of base, preferably potassium carbonate provides the enol ether 18. Treatment of 18 with a brominating agent such as NBS in acetone, gives the bromoketone 19 which can then be alkylated with either aryl thiols (20, X=S) or substituted phenols (20, X=O) to afford the ketones 21. Ketones 21, wherein Y is a covalent bond could also be prepared from 19 in a two step procedure, first alkylating with either bromo thiophenols (20a, X=S) or bromophenols (20a, H=O), then coupling the aryl bomides 10a with an appropriate aryl boronic acid following the Suzuki protocol, or an appropriate aryl stannane. The reaction sequence described in scheme 1 can then be used to convert 21 into the hydroxamic acids 22. The compounds wherein X = S can be converted to the sulfones 23 via oxidation with an appropriate oxidant such as m-chloroperbenzoic acid or oxone.

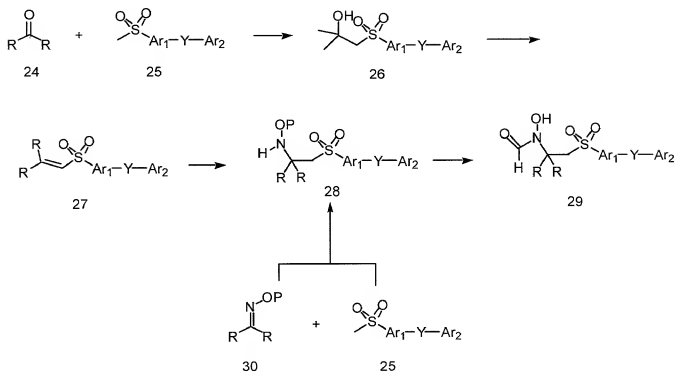
Scheme 4



Scheme 5 shows an alternate synthesis of the sulfones 29. Deprotonation of the sulfone 25 with a base such as LDA followed by addition to a ketone or aldehyde 24 gives an alcohol which can be dehydrated either by reaction with acid, such as toluene sulfonic acid or by a stepwise 2 step procedure: first convering the alcohol into a leaving group, such as mesylate via treatment with mesyl chloride and triethyl amine, then eliminating with a base, preferably 1,8-diazabicyclo[5.4.0]undec-7-ene. Reaction of the olefin with an O-protected hydroxylamine preferably O-benzyl gives the adduct 28. Formylation as previously described in scheme 1 followed by removal of the protecting group, preferably under hydrogenation conditions for the compounds wherein P is benzyl affords the sulfone 29. The sulfone 28 can also be prepared directly via the deprotonation of sulfone 25, with

a base such as n-BuLi and subsequent addition, preferably in the presence of boron trifluoride etherate, to a O-protected oxime 30.

Scheme 5



The foregoing may be better understood by reference to the following examples which illustrate the methods by which the compounds of the invention may be prepared and are not intended to limit the scope of the invention as defined in the appended claims.

Example 1

(\pm) -N-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-phenoxyethyl]-N-hydroxyformamide

Example 1A

(\pm) -3-Phenoxypropan-[1,2]oxirane

A suspension of sodium hydride (0.47 g, 11.7 mmol) in THF (20 mL) was treated sequentially with a solution of phenol (1.00 g, 10.6 mmol) in THF (20 mL) then epibromohydrin (2.73 mL, 31.8 mmol) in a single portion, refluxed for 2 hours, cooled, treated with 20% aqueous potassium hydrogen sulfate then partitioned between ethyl acetate and brine. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), filtered, and concentrated to provide 1.65 g

of a golden oil which was purified on silica gel with 10% ethyl acetate/hexanes (500 mL) and 20% ethyl acetate/hexanes to provide 1.19 g (75%) of the title compound.
MS (DCI/NH₃) m/e 168 (M+NH₄)⁺ and 185 (M+NH₄+NH₃)⁺.

Example 1B

([±])-1-(4-(4'-Carbonitrilephenyl)phenoxy)-3-phenoxy-2-propanol

A suspension of sodium hydride (0.18 g, 4.39 mmol) in THF (4 mL) was treated sequentially with a solution of 4'-hydroxy-4-biphenylcarbonitrile (0.78 g, 3.99 mmol) in THF (4 mL), Example 1A (0.60 g, 3.99 mmol) in THF (2 mL) then DMF (6 mL), refluxed for 1 hour, cooled, treated with 20% aqueous potassium hydrogen sulfate and partitioned between ethyl acetate and brine. The organic layer was washed with saturated aqueous sodium bicarbonate, 15% aqueous sodium hydroxide and brine, dried (Na₂SO₄), filtered, and concentrated to provide 1.04 g of a yellow oil which was purified on silica gel with 25-30% ethyl acetate/hexanes to provide 0.42 g (22%) of the title compound.
MS (DCI/NH₃) m/e 363 (M+NH₄)⁺ and 380 (M+NH₄+NH₃)⁺.

Example 1C

([±])-N,O-bis(t-butyloxycarbonyl)-1-(4-(4'-carbonitrilephenyl)phenoxy)-3-phenoxy-prop-2-yl-N-hydroxylamine

A solution of Example 1B (0.41 g, 1.19 mmol), triphenylphosphine (0.40 g, 1.54 mmol), and di-Boc-hydroxylamine (0.33 g, 1.42 mmol) in THF (5 mL) was treated dropwise with diethylazodicarboxylate (0.24 mL, 1.54 mmol), stirred at ambient temperature for 1 hour and concentrated. The resulting oil was redissolved in dichloromethane (30 mL) and concentrated under vacuum (2 cycles) to remove any excess THF then purified on silica gel with 15% ethyl acetate/hexanes to provide 0.50 g (75%) of the title compound as a colorless foam.
MS (DCI/NH₃) m/e 578 (M+NH₄)⁺.

Example 1D

([±])-1-(4-(4'-Carbonitrilephenyl)phenoxy)-3-phenoxy-prop-2-yl-N-hydroxylamine

A solution of Example 1C (0.45 g; 0.80 mmol) in dichloromethane (3 mL) was treated with trifluoroacetic acid (6 mL), stirred for 15 minutes at ambient temperature, poured into excess saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The resulting organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated to provide 0.70 g of a brown oil which was purified on silica gel with 50% ethyl acetate/hexanes to provide 0.23 g (81%) of deprotected hydroxylamine as a light yellow foam.

Example 1E

([±])-*N*-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-phenoxyethyl]-*N*-hydroxyformamide

A solution of Example 1D (0.15 g, 0.41 mmol) in dichloromethane (2 mL) was cooled to -10 °C and treated with a solution of formicacetyl anhydride (38 mg, 0.43 mmol) in dichloromethane (1 mL), stirred for 15 minutes, diluted with ether and washed sequentially with saturated aqueous sodium bicarbonate, 10% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and brine, dried (Na₂SO₄), filtered, and concentrated to provide 0.17 g of a brown, glassy oil which was purified on silica gel with 97.5% (40% ethyl acetate/hexanes)/2.5% methanol to provide 67 mg (42%) of light brown foam which was recrystallized from ethyl acetate/hexanes/acetone to provide the title compound as light pink, clumpy crystals.

mp 133-135 °C;

¹H NMR (300 MHz, CDCl₃) δ 8.15 (br s; 1H), 8.07 (s; 1H), 7.69 (AB; 1H; J=9 Hz), 7.62 (AB; 1H; J=9 Hz), 7.54 (d; 1H; J=9 Hz), 7.32 (dd; 1H; J=6.5, 8.0 Hz), 6.97-7.06 (m; 3H), 6.92 (d; 2H; J=7.5 Hz), 4.24-4.47 (m; 5H);

MS (DCI/NH₃) m/e 345 (M+NH₄-HCONHOH)⁺;

Anal. calcd for C₂₃H₂₀N₂O₄: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.04; H, 5.16; N, 7.01.

Example 2

([±])-*N*-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(phenylthio)ethyl]-*N*-hydroxyformamide

Example 2A

([±])-3-(4-(4'-Carbonitrilephenyl)phenoxy)propan-[1,2]oxirane

The title compound was prepared following the procedure from Example 1A but using 4'-hydroxy-4-biphenylcarbonitrile (10.0 g, 51.2 mmol) in place of phenol.

Purification by trituration with ether provided 9.13 g (71%) the title compound as a chalky solid.

mp 115-116 °C;

MS (DCI/NH₃) m/e 269 (M+NH₄)⁺ and 286 (M+NH₄+NH₃)⁺.

Example 2B

([±])-1-(4-(4'-Carbonitrilephenyl)phenoxy)-3-thiophenoxy-2-propanol

09905242.071601

A solution of Example 2A (0.90 g), triethylamine (1.75 mL), and benzenethiol (1.10 mL) in absolute ethanol (14 mL) was heated at reflux for 1 hour, cooled and partitioned between ethyl acetate and 10% aqueous sodium hydroxide. The organic layer was washed sequentially with 10% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and brine, dried (Na₂SO₄), filtered, and concentrated to provide 1.27 g of a thick golden oil which was purified by recrystallization from ethyl acetate/hexanes/methanol to provide the title compound as colorless, clumpy crystals. mp 105-106 °C; MS (DCI/NH₃) m/e 379 (M+NH₄)⁺.

Example 2C

([±])-1-(4-(4'-Carbonitrilephenyl)phenoxy)-3-thiophenoxy-2-propanone

A suspension of the Dess-Martin periodinane in dichloromethane (25 mL) was treated with Example 2B (2.02 g) in dichloromethane (15 mL), stirred at ambient temperature for 0.5 hours and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed sequentially with saturated aqueous sodium thiosulfate, saturated aqueous sodium bicarbonate and brine, dried (Na₂SO₄), filtered, and concentrated to provide 2.27 g of a clumpy, orange solid which was purified on silica gel with 30% ethyl acetate/hexanes to provide 1.90 g of the title compound as a chalky, light yellow solid. MS (DCI/NH₃) m/e 377 (M+NH₄)⁺.

Example 2D

([±])-1-(4-(4'-Carbonitrilephenyl)phenoxy)-3-thiophenoxy-2-propanone oxime

A solution of Example 2C (2.02 g) in methanol (20 mL) and THF (10 mL) was treated sequentially with 10 drops of pyridine then hydroxylamine-hydrochloride (0.78 g), heated at reflux for 1 hour, cooled and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed sequentially with water and brine, dried (Na₂SO₄), filtered, and concentrated to provide 1.90 g of the title compound as a chalky yellow solid which was used without further purification. MS (DCI/NH₃) m/e 375 (M+H)⁺ and 392 (M+NH₄)⁺.

Example 2E

([±])-N-(4-(4'-carbonitrilephenyl)phenoxy)-3-thiophenoxyprop-2-yl)hydroxylamine

A solution of Example 2D (1.90 g) in THF (10 mL) was treated sequentially with absolute ethanol (20 mL), borane-pyridine (1.5 mL) then dropwise with 6N aqueous hydrochloric acid, stirred for 1 hour at ambient temperature, poured into excess saturated

aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated to provide 2.25 g of an orange oil which was purified on silica gel with 30% ethyl acetate/hexanes to provide 1.26 g of the title compound as a light gold oil.

5 MS (DCI/NH₃) m/e 377 (M+H)⁺ and 394 (M+NH₄)⁺.

Example 2F

([±])-N-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(phenylthio)ethyl]-N-hydroxyformamide

10 A solution of compound 2E (1.24 g) in THF (10 mL) was cooled to -23 °C and treated with a solution of formicacetylanhydride (280 μL) in THF (2 mL), stirred for 15 minutes, diluted with ether. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate, 10% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and brine, dried (Na₂SO₄), filtered, and concentrated to provide 1.27 g of a
15 glassy orange oil which was purified on silica gel with 97.5% (40% ethyl acetate/hexanes)/2.5% methanol to provide 300 mg of the title compound as a light orange foam.

¹H NMR (300 MHz, CDCl₃) δ 7.95 (br s; 1H), 7.90 (s; 1H), 7.70 (AB; 1H; J=7.5 Hz), 7.62 (AB; 1H; J=7.5 Hz), 7.51 (d; 1H; J=9 Hz), 7.20-7.43 (m; 5H), 6.95 (d; 2H; J=9 Hz), 4.33 (dd; 1H; J=8.5, 10.5 Hz), 4.17 (dd; 1H; J=4.5, 10.5 Hz), 4.0 (m; 1H), 3.36 (dd; 1H; J=8.5, 14 Hz), 3.28 (dd; 1H; J=6, 14 Hz);

20 MS (DCI/NH₃) m/e 422 (M+NH₄)⁺.

Anal. calcd for C₂₃H₂₀N₂O₃S: C, 68.30; H, 4.98; N, 6.73. Found: C, 68.19; H, 4.86; N, 6.73.

Example 3

([±])-N-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)ethyl]-N-hydroxyformamide

Example 3A

([±])-3-(4-(4'-Carbonitrilephenyl)phenoxy)-3-iodo-2-propanol

30 A solution of iodine (1.54 g, 6.0 mmol) in dichloromethane (20 mL) was treated with triphenylphosphine (1.58 g, 6.0 mmol), stirred for 5 minutes, treated with 3-(4'-carbonitrilephenyl)phenoxy)propan-(1,2) oxirane (1.0 g, 4.0 mmol) in a single portion,
35 stirred at ambient temperature for 30 minutes, treated with water and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated

to provide 3 g of crude product which was purified on silica gel with 30% ethyl acetate/hexanes to provide 1.38 g (91%) of the title compound. MS (DCI/NH₃) m/e 397 (M+NH₄)⁺ and 414 (M+NH₄+NH₃)⁺.

5

Example 3B

3-(4-(4'-Carbonitrilephenyl)phenoxy)-1-iodopropan-2-one

The title compound was prepared as in Example 2C but using Example 3A (1.0 g, 2.63 mmol) in place of 3-(4-(4'-carbonitrilephenyl)phenoxy)-1-thiophenoxypropan-2-ol.

10 Purification on silica gel with 20% ethyl acetate/hexanes provided 0.65 g (66%) of the title compound.

MS (DCI/NH₃) m/e 395 (M+NH₄)⁺ and 412 (M+NH₄+NH₃)⁺.

Example 3C

1-(4-(4'-Carbonitrilephenyl)phenoxy)-3-phthaloylpropan-2-one

A solution of Example 3B (1.38 g; 3.66 mmol) in DMF (20 mL) was treated with potassium phthalimide (1.02 g; 5.50 mmol), stirred at ambient temperature for 10 minutes, treated with water and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to provide 1.1 g of crude product which was

20 purified on silica gel with ethyl acetate to provide 0.98 g (67%) of the title compound. MS (DCI/NH₃) m/e 414 (M+NH₄)⁺.

Example 3D

([±])-N-[1-[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)ethyl]-N-hydroxyformamide

25

The title compound was prepared according to Example 2D but using Example 3C (0.56 g, 1.41 mmol) in place of 1-(4-(4'-carbonitrilephenyl)phenoxy)-3-thiophenoxypropan-2-one to provide the corresponding oxime which was reduced according to Example 2E using 1-(4-(4'-carbonitrilephenyl)phenoxy)-3-phthaloylpropan-2-one oxime in place of 1-(4-(4'-carbonitrilephenyl)phenoxy)-3-thiophenoxypropan-2-one oxime. The resulting hydroxylamine was formylated according to Example 2F but using 1-(4-(4'-carbonitrilephenyl)phenoxy)-3-phthaloyl-2-propylhydroxylamine in place of 1-(4-(4'-carbonitrilephenyl)phenoxy)-3-thiophenoxy-2-propylhydroxylamine. Purification on silica gel with 60% ethyl acetate/hexanes provided 0.185 g (30%) of the title compound.

35 mp 199-202 °C;

¹H NMR (300 MHz, CDCl₃) δ 10.06 (s; 0.5H), 9.67 (s; 0.5H), 8.32 (s; 0.5H), 7.99 (s; 0.5H), 7.88 (m; 8H), 7.72 (m; 2H), 7.02 (m; 3H), 4.96 (m; 0.5H), 4.52 (m; 0.5H), 4.25 (m; 2H), 3.78-4.00 (m; 2H);
MS (DCI/NH₃) m/e 459 (M+NH₄)⁺;
5 Anal. calcd for C₂₅H₁₉N₃O₅: C, 67.96; H, 4.304; N, 9.51. Found: C, 67.43; H, 4.34; N, 9.04.

Example 4

10 ([±])-N-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxoimidazolidiny-1-yl)ethyl]-N-hydroxyformamide

Example 4A

([±])-1-(4-(4'-Carbonitrilephenyl)phenoxy)-3-((5,5-dimethyl)hydantoin-3-yl)-2-propanol

15 A solution of 5,5-dimethylhydantoin (0.26 g, 1.99 mmol) in THF (20 mL) was treated with potassium tert-butoxide (1.99 mL, 1.99 mmol), stirred for 5 minutes, treated with 3-(4'-carbonitrilephenyl)phenoxy)-(1,2) oxirane (0.50 g, 1.99 mmol) in a single portion, stirred at 70 °C for 6 hours, treated with excess saturated aqueous ammonium chloride and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to provide a yellow solid which was purified on silica
20 gel with ethyl acetate to provide 0.70 g (93%) of the title compound.
MS (DCI/NH₃) m/e 397 (M+NH₄)⁺.

Example 4B

25 ([±])-1-(4-(4'-Carbonitrilephenyl)phenoxy)-3-(3-(5,5-dimethyl)hydantoin)-2-(t-butyl)dimethylsilyloxy)propane

A solution of Example 4A (0.40 g, 1.06 mmol) in dichloromethane (20 mL) was treated with tert-butyldimethylsilyl chloride (0.24 g, 1.60 mmol) and imidazole (0.1 g, 1.6 mmol), stirred at ambient temperature for 30 minutes, treated with water and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and
30 concentrated to provide a solid which was purified on silica gel with 50% ethyl acetate/hexanes to provide 0.50 g (95%) of the title compound.
MS (DCI/NH₃) m/e 511 (M+NH₄)⁺.

Example 4C

35 ([±])-1-(4'-Cyano-[1,1'-biphenyl]-4-yl)oxy)-3-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidin-1-yl)-2-t-butyl)dimethylsilyloxypropane

A solution of 4B (0.60 g, 1.20 mmol) in THF (20 mL) was treated with sodium hydride (0.035g, 1.40 mmol) then iodomethane (0.26g, 1.8 mmol) in a single portion, stirred at 70 °C for 30 minutes, treated with saturated aqueous ammonium chloride and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄),

5 filtered, and concentrated to provide the title compound as white crystals.

Example 4D

(⁺)-1-(4'-Cyano-[1,1'-biphenyl]-4-yl)oxy)-3-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidin-1-yl)-2-propanol

10 A solution of Example 4C in THF (30 mL) was treated with tetrabutylammonium fluoride (1M in THF, 2.0 mL, 2.0 mmol), stirred at ambient temperature for 30 minutes, treated with water and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to provide crude product which was purified on silica gel with ethyl acetate to provide 0.47 g (100%) of the title compound.

15 MS (DCI/NH₃) m/e 411 (M+NH₄)⁺.

Example 4E

1-(4'-Cyano-[1,1'-biphenyl]-4-yl)oxy)-3-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)-2-propanone

20 Example 4D (0.59 g, 1.50 mmol) was processed according to the procedure in Example 2C. Purification of the crude product on silica gel with 50% ethyl acetate/hexanes provided 0.58 g (98%) of the title compound.

MS (DCI/NH₃) m/e 409 (M+NH₄)⁺.

Example 4F

25 (⁺)-[1-(4'-Cyano-[1,1'-biphenyl]-4-yl)oxy)-3-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)-prop-2-yl]hydroxylamine

Example 4E (0.57 g, 1.46 mmol) was processed according to the procedures in Examples 2D and 2E. Purification of the crude product on silica gel with 60% ethyl acetate/hexanes provide 0.31 g (52%) of the title compound.

30 MS (DCI/NH₃) m/e 409 (M+H)⁺.

Example 4G

(⁺)-N-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-N-hydroxyformamide

35

Example 4F was processed according to the procedure in Example 2F. Purification of the crude product on silica gel with 60% ethyl acetate/hexanes provided 0.19 g (60%) of the title compound.

mp 65-67 °C;

5 MS (DCI/NH₃) m/e 437 (M+H)⁺ and 454 (M+NH₄)⁺.

¹H NMR (300 MHz, CDCl₃) δ 9.90 (s; 0.5H), 9.58 (s; 0.5H), 8.32 (s; 0.5H), 7.92 (s; 0.5H), 7.85 (m; 4H), 7.72 (d; 2H; J=5.6 Hz), 7.02 (dd; 2H; J=5.5, 2.5 Hz), 4.86 (m; 0.5H), 4.42 (m; 0.5H), 4.08-4.02 (m; 2H), 3.82-3.70 (m; 1H), 3.55-4.05 (m; 1H), 2.8 (s; 1.5H), 2.78 (s; 1.5H), 1.5 (s; 3H), 1.48 (s; 3H);

10 Anal. calcd for C₂₃H₂₄N₄O₅: C, 63.23; H, 5.50; N, 12.83. Found: C, 62.96; H, 5.55; N, 12.45.

Example 5

([±])-N-[1-[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-3-(3,4,4-trimethyl-2,5-dioxoimidazolidiny-1-yl)propyl]-N-hydroxyformamide

15

Example 5A

1-(Prop-2-enyl)-4,4-dimethyl-2,5-dioxoimidazolidine

A solution of 3-buten-1-ol (1 g, 13.9 mmol), triphenylphosphine (4.73 g, 18 mmol) and 5,5-dimethylhydantoin (2.1 g, 16.7 mmol) in THF (50 mL) was treated dropwise with diethylazodicarboxylate (3.13 g, 18.0 mmol), stirred at ambient temperature for 1 hour, treated with water and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to provide crude product which was purified on silica gel with 50% ethyl acetate/hexanes to provide 2.5 g (100%) of the title compound.

25

Example 5B

1-(Prop-2-enyl)-3,4,4-trimethyl-2,5-dioxoimidazolidine

A solution of Example 5A (2.3 g, 12.6 mmol) in THF (50 mL) was treated with sodium hydride (0.45 g, 18.9 mmol) then iodomethane (2.7 g, 18.9 mmol) in a single portion, refluxed for 2 hours, cooled, treated with water, and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to provide 3.5 g of a yellow solid which was purified on silica gel with 50% ethyl acetate/hexanes to provide 2.4 g (98%) of the title compound.

30

MS (DCI/NH₃) m/e 214 (M+NH₄)⁺.

Example 5C

([±])-1-((1',2'Oxiranyl)propyl)-3,4,4-trimethyl-2,5-dioxoimidazolidine

09905242-071601

A solution of Example 5B (3.0 g, 15.3 mmol) in dichloromethane (50 mL) was treated with m-chloroperbenzoic acid (4.4 g), stirred at ambient temperature for 2 hours, treated with saturated aqueous sodium carbonate and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to a solid which

5 was purified on silica gel with 70% ethyl acetate/hexanes to provide 1.5 g (46%) of the title compound.

MS (DCI/NH₃) m/e 213 (M+1)⁺ and 230 (M+NH₄)⁺.

Example 5D

(⁺)-1-(2-Hydroxy-3-iodo-propyl)-3,4,4-trimethyl-2,5-dioxoimidazolidine

10 A solution of iodine (0.29 g, 1.88 mmol) in dichloromethane (20 mL) was treated with triphenylphosphine (0.3 g, 1.88 mmol), stirred for 5 minutes, treated with Example 5C (0.2 g, 0.94 mmol) in a single portion, stirred at ambient temperature for 30 minutes, treated with water and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to provide a yellow solid which was purified on silica gel with 75% ethyl acetate/hexanes to provide 0.26 g (80%) of the title compound.

15 MS (DCI/NH₃) m/e 342 (M+H)⁺ and 358 (M+NH₄)⁺.

Example 5E

1-(3-Iodo-propan-2-onyl)-3,4,4-trimethyl-2,5-dioxoimidazolidine

20 Example 5D was processed according to the procedure in Example 2C. Purification the crude product on silica gel with 60% ethyl acetate/hexanes provided 0.3 g (96%) of the title compound.

MS (DCI/NH₃) m/e 339 (M+H)⁺ and 356 (M+NH₄)⁺.

Example 5F

(⁺)-1-(3-[(4'-Cyano-[1,1'-biphenyl]-4-yl)oxy]-propan-2-on-1-yl)-3,4,4-trimethyl-2,5-dioxoimidazolidine

25 A solution of 4'-hydroxy-4-biphenylcarbonitrile (0.38 g, 1.9 mmol) in THF (50 mL) was treated with potassium carbonate (0.5 g) then Example 5E (0.44 g, 1.30 mmol), refluxed for 7 hours, cooled, treated with 10% aqueous HCl and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to provide a yellow solid which was purified on silica gel with 75% ethyl acetate/hexanes to provide 0.52 g (99%) of the title compound.

35 MS (DCI/NH₃) m/e 423 (M+NH₄)⁺.

Example 5G

([±])-1-(3-[(4'-Cyano-[1,1'-biphenyl]-4-yl)oxy]-propan-2-oximino-1-yl)-3,4,4-trimethyl-
2,5-dioxoimidazolidine

Example 5F was processed according to the procedure in Example 2D. The crude product was purified on silica gel with 75% ethyl acetate/hexanes to provide 0.68 g (1.60 mmol; 100%) of the title compound.
MS (DCI/NH₃) m/e 439 (M+NH₄)⁺.

Example 5H

([±])-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-3-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)propyl]-N-hydroxyformamide

Example 5G was processed according to the procedures in Examples 2E and 2F. Purification of the crude product on silica gel with 75% ethyl acetate/hexanes provided 0.408 g (56%) of the title compound.

mp 68-70 °C;

¹H NMR (300 MHz, CDCl₃) δ 9.99 (s; 0.5H), 9.46 (s; 0.5H), 8.35 (s; 0.5H), 7.92 (s; 0.5H), 7.92 (d; 2H; J=5.6Hz), 7.85 (d; 2H; J=5.6Hz), 7.70 (d; 2H; J=5.6 Hz), 7.05 (d; 2H; J=5.6Hz), 4.52 (m; 0.5H), 4.18-3.95 (m; 3.5H), 3.46 (m; 2H), 2.82 (s; 1.5H), 2.79 (s; 1.5H), 2.02-1.72 (m; 1H), 1.32 (s; 6H);

MS (DCI/NH₃) m/e 468 (M+NH₄)⁺;

Anal. calcd for C₂₄H₂₆N₄O₅: C, 63.93; H, 5.77; N, 12.43. Found: C, 63.38; H, 5.99; N, 11.97.

Example 6

([±])-N-[1-[[[3'-(cyanomethyl)-[1,1'-biphenyl]-4-yl]oxy]methyl]pentyl]-N-hydroxyformamide

Example 6A

4-((t-Butyldimethyl)silyloxy)phenyl boronic acid

A solution of (4-bromophenoxy)trimethylsilane (69 g, 20.9 mmol) in THF (60 mL) was treated with n-butyllithium at -78 °C, stirred for 15 minutes, treated with triisopropyl borate, stirred at -78 °C for 10 minutes, warmed to ambient temperature, stirred for another 30 minutes, treated with water and partitioned between ethyl acetate and brine. The organic layer was dried (MgSO₄), filtered, and concentrated to provide 4.79 g (91%) of the title compound.

Example 6B

4'-Hydroxy-3-biphenylcarbonitrilemethane

A mixture of Example 6A (4.8 g, 19.0 mmol), 3-bromophenyl acetonitrile (3.1 g, 16.0 mmol), cesium carbonate (7.8 g, 24.0 mmol) and tetrakis(triphenylphosphine)-palladium(0) (0.55 g, 0.48 mmol) was treated via syringe with DMF (30 mL) under positive nitrogen pressure, stirred at 100 °C for 10 h, treated with water and partitioned between ethyl acetate and brine. The organic layer was dried (MgSO₄), filtered, and concentrated to provide a brown oil which was purified on silica gel with 50% ethyl acetate/hexanes to provide 3.3 g (82%) of the title compound. MS (DCI/NH₃) m/e 227 (M+NH₄)⁺.

Example 6C

Ethyl 2-(4-(3'-carbonitrilemethylphenyl)phenoxy)acetate

A solution of 6B (0.5 g, 2.4 mmol) in THF (20 mL) was treated with potassium carbonate (0.5 g) and ethyl bromoacetate (0.6 g, 3.6 mmol), refluxed for 3 hours, cooled, treated with 10% aqueous HCl and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to provide a yellow solid which was purified on silica gel with 50% ethyl acetate/hexanes to provide 0.48 g (68%) of the title compound.

¹H NMR (300 MHz, CDCl₃) δ 7.52 (m; 4H), 7.40 (m; 1H), 7.36 (m; 1H), 7.0 (m; 2H), 4.65 (s; 2H), 4.30 (q; 2H; J=4.8 Hz), 3.80 (s; 2H), 1.32 (t; 3H; J=4.8Hz).

Example 6D

2-(4-(3'-Carbonitrilemethylphenyl)phenoxy)acetic acid

A solution of 6C (0.47 g, 1.6 mmol) in 1,4-dioxane (20 mL) and water (10 mL) was treated with lithium hydroxide (0.5 g), stirred at ambient temperature for 30 minutes, treated with 10% aqueous HCl and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to provide a yellow solid which was purified on silica gel with 50% ethyl acetate/hexanes to provide 0.37 g (83%) of the title compound.

¹H NMR (300 MHz, CDCl₃) δ 7.60 (m; 4H), 7.46 (m; 1H), 7.32 (m; 1H), 7.02 (m; 2H), 4.72 (s; 2H), 4.08 (s; 2H).

Example 6E

N,O-dimethyl-2-(4-(3'-carbonitrilemethylphenyl)phenoxy)acetyl hydroxylamine

A solution of 6D (0.35 g, 1.3 mmol), triethylamine (0.5 mL) and bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (0.78 g, 2.6 mmol) in dichloromethane (20 mL) was treated with N,O-dimethyl-hydroxylamine hydrochloride (0.25 g, 2.6 mmol), stirred at

09905242-071601

ambient temperature for 2 hours, treated with water and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to provide a yellow solid which was purified on silica gel with 50% ethyl acetate/hexanes to provide 0.28 g (69%) of the title compound.

- 5 ¹H NMR (300 MHz, CDCl₃) δ 7.59 (m; 4H), 7.46 (m; 1H), 7.32 (m; 1H), 7.02 (m; 2H), 4.96 (s; 2H), 4.08 (s; 2H), 3.78 (s; 3H), 3.15 (s; 3H).

Example 6F

1-(4-(3'-(Carbonitrilemethyl)phenyl)phenoxy)-2-hexanone

- 10 A solution of 6E (0.27 g, 0.85 mmol) in THF (10 mL) was treated with n-butyilmagnesium bromide (1 mL, 2.0 mmol) at -78 °C, stirred at -78 °C for 1 h, treated with water and partitioned between ethyl acetate and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated to provide a yellow solid which was purified on silica gel with 25% ethyl acetate/hexanes to provide 0.15 g (59%) of the title compound.
- 15 ¹H NMR (300 MHz, CDCl₃) δ 7.52 (m; 4H), 7.42 (m; 1H), 7.28 (m; 1H), 6.98 (m; 2H), 4.60 (s; 2H), 3.82 (s; 2H), 2.62 (t; 2H; J=5.5 Hz), 1.64 (m; 2H), 1.38 (m, 2H), 0.92 (t; 3H; J=4.8Hz).

Example 6G

- 20 (±)-N-[1-[[[3'-(cyanomethyl)-[1,1'-biphenyl]-4-yl]oxy]methyl]pentyl]-N-hydroxyformamide

Example 6F (0.15 g, 0.50 mmol) was processed according to the procedures described in Examples 2D-F (inclusive). Purification of the crude final product on silica gel with 40% ethyl acetate/hexanes provided 0.07 g (41%) of the title compound.

- 25 mp 99-101 °C;
MS (DCI/NH₃) m/e 352 (M+NH₄)⁺.
¹H NMR (300 MHz, CDCl₃) δ 8.58 (brs; 0.5H), 8.04 (brs; 0.5H), 8.0 (s; 1H), 7.48 (m; 4H), 7.42 (m; 1H), 7.26 (m; 1H), 6.98 (m; 2H), 4.05 (t; 1H; J=5.6 Hz), 3.8-4.0 (m; 2H), 3.80(s; 2H), 1.92 (m; 1H), 1.60 (m; 2H), 1.38 (m; 3H), 0.98 (t; 3H; J=4.8 Hz).
- 30 Anal. calcd for C₂₁H₂₄N₂O₃: C, 71.50; H, 6.81; N, 7.94. Found: C, 71.44; H, 6.90; N, 7.80.

Example 7

- 35 (±)-N-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-3-methylbutyl]-N-hydroxyformamide

4'-hydroxy-4-biphenylcarbonitrile (1.0 g, 5.12 mmol) was processed according to the procedures described in Examples 6C-G (inclusive), but substituting isobutylmagnesium bromide for the n-butylmagnesium bromide used in Example 6F.

Purification of the crude final product on silica gel with 30% ethyl acetate/hexanes

provided 0.036 g of the title compound.

mp 112-113 °C;

MS (DCI/NH₃) m/e 356 (M+NH₄)⁺.

¹H NMR (300 MHz, CDCl₃) δ 7.95 (s; 1H), 7.70 (d; 2H; J=5.6 Hz), 7.62 (d; 2H; J=5.8),

7.52 (d; 2H; J=5.8 Hz), 6.98 (d; 2H; J=5.8Hz), 4.25 (m; 1H), 3.92-4.05 (m; 2H), 1.95 (m;

1H), 1.75 (m; 1H), 1.35(m; 1H), 1.00 (d; 3H; J=4.8 Hz), 0.98 (d; 3H; J=4.8 Hz).

Anal. calcd for C₂₀H₂₂N₂O₃: C, 70.92; H, 6.50; N, 8.27. Found: C, 70.91; H, 6.68; N, 8.13.

Example 8

(⁺)-N-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-methylbutyl]-N-hydroxyformamide

The title compound was prepared following the sequence of steps described in Example 7 but substituting sec-butylmagnesium chloride for isobutylmagnesium bromide.

Purification of the crude final product on silica gel with 30% ethyl acetate/hexanes

provided 0.10 g of the title compound.

mp 96-98 °C;

MS (DCI/NH₃) m/e 356 (M+NH₄)⁺.

¹H NMR (300 MHz, CDCl₃) δ 7.95 (s; 1H), 7.70 (d; 2H; J=5.6 Hz), 7.62 (d; 2H; J=5.8),

7.52 (d; 2H; J=5.8 Hz), 6.98 (d; 2H; J=5.8Hz), 4.32 (m; 1H), 4.15 (m; 2H), 3.65 (m; 1H),

1.98 (m; 1H), 1.62 (m; 1H), 1.02 (m; 3H), 0.98 (m; 3H);.

Anal. calcd for 0.8 H₂O+C₂₀H₂₂N₂O₃: C, 68.03; H, 6.69; N, 7.90. Found: C, 68.60 ; H, 6.58; N, 7.23.

Example 9

(⁺)-N-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]pentyl]-N-hydroxyformamide

The title compound was prepared following the sequence of steps described in

Example 7 but substituting n-butylmagnesium bromide for isobutylmagnesium bromide.

Purification of the crude final product on silica gel with 30% ethyl acetate/hexanes

provided 0.210 g of the title compound.

mp 105-108 °C;

MS (DCI/NH₃) m/e 356 (M+NH₄)⁺.

¹H NMR (300 MHz, CDCl₃) δ 7.95 (s; 1H), 7.70 (d; 2H; J=5.6 Hz), 7.62 (d; 2H; J=5.8), 7.52 (d; 2H; J=5.8 Hz), 6.98 (d; 2H; J=5.8Hz), 4.25 (m; 1H), 3.99-3.82 (m; 2H), 1.92 (m; 1H), 1.60 (m; 2H), 1.40 (m; 3H), 0.98 (t; 3H; J=4.3Hz).

Anal. calcd for 0.5C₆H₆+C₂₀H₂₂N₂O₃: C, 73.13; H, 6.62; N, 7.42. Found: C, 73.18 ; H, 6.65; N, 7.39.

Example 10

([±])-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(4-methylphenyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the sequence of steps described in Example 7 but substituting 4-methylbenzylmagnesium bromide for isobutylmagnesium bromide. Purification of the crude final product on silica gel with 30% ethyl acetate/hexanes provided 0.24 g of the title compound.

mp 173-175 °C;

MS (DCI/NH₃) m/e 404 (M+NH₄)⁺.

¹H NMR (300 MHz, CDCl₃) δ 7.70 (d; 2H; J=5.6 Hz), 7.68 (s; 1H), 7.62 (d; 2H; J=5.8), 7.52 (d; 2H; J=5.8 Hz), 7.12 (s; 4H), 6.98 (d; 2H; J=5.8Hz), 4.35 (m; 1H), 4.12-3.98 (m; 2H), 3.15 (m; 1H), 2.94 (m; 1H), 1.35 (s; 3H).

Anal. calcd for C₂₄H₂₂N₂O₃: C, 74.52; H, 5.69; N, 7.24. Found: C, 73.95 ; H, 5.79; N, 7.06.

Example 11

([±])-N-[2-[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]-1-(4-fluorophenyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the sequence of steps described in Example 7, but substituting 4-fluorophenylmagnesium bromide for isobutylmagnesium bromide. Purification of the crude final product on silica gel with 30% ethyl acetate/hexanes provided 0.285 g of the title compound.

mp 194-196 °C;

MS (DCI/NH₃) m/e 394 (M+NH₄)⁺;

¹H NMR (300 MHz, CDCl₃) δ 9.70 (brs; 1H), 8.42 (s; 0.5H), 8.28 (s; 0.5H), 7.86 (m; 4H), 7.72 (d; 2H; J=5.6 Hz), 7.55 (m; 2H), 7.25 (m; 2H), 7.12 (d; 2H; J=5.8 Hz), 5.72 (brs; 0.5H), 5.35 (brs; 0.5H), 4.60 (m; 1H), 4.36 (m; 1H);

Anal. calcd for C₂₂H₁₇N₂O₃F: C, 70.14; H, 4.45; N, 7.44. Found: C, 70.19 ; H, 4.25; N, 7.30.

Example 12

([±])-*N*-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4-fluorophenyl)ethyl]-*N*-hydroxyformamide

The title compound was prepared following the sequence of steps described in Example 7 but substituting 4-fluorobenzylmagnesium bromide for isobutylmagnesium bromide. Purification of the crude final product on silica gel with 30% ethyl acetate/hexanes provided 0.22 g of the title compound.

MS (DCI/NH₃) m/e 408 (M+NH₄)⁺;

¹H NMR (300 MHz, CDCl₃) δ 8.35 (brs; 1H), 7.65 (m; 5H), 7.52 (d; 2H; J=5.6 Hz), 7.20 (m; 2H), 6.98 (m; 4H), 4.35 (m; 1H), 4.15-3.98 (m; 2H), 3.18 (dd; 1H; J=6.0, 9.0 Hz), 2.95 (dd; 1H; J=3.0, 9.0 Hz);

Anal. calcd for C₂₃H₁₉N₂O₃F: C, 70.69; H, 4.87; N, 7.17. Found: C, 70.38 ; H, 4.96; N, 6.98.

Example 13

([±])-*N*-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]ethyl]-*N*-hydroxyformamide

Example 13A

(4-(4'-Carbonitrilephenyl)phenoxy)propan-2-one

A solution of 4-(4'-carbonitrilephenyl)phenol (4.86 g, 24.9 mmol) in DMF (100 mL) was treated with potassium carbonate (13.8 g, 99.6 mmol), heated at 50 °C for 10 minutes, treated in a single portion with chloroacetone (2.48 mL, 30 mmol), stirred for 4 hours at ambient temperature and partitioned between 3:1 ether:hexanes and saturated aqueous sodium carbonate. The organic layer was dried (MgSO₄), filtered, and concentrated under vacuum to 1/3 of its original volume to cause precipitation of product from solution. The solution was treated with more ether and stored at -20 °C for 17 hours. The title compound (2.01 g, 32%) was collected by filtration and dried under vacuum. MS (DCI/NH₃) m/e 251 (M)⁺, 269 (M+NH₄)⁺ and 286 (M+NH₄+NH₃)⁺.

Example 13B

([±])-*N*-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]ethyl]-*N*-hydroxyformamide

The title compound was obtained following the procedures in Examples 2D-F (inclusive) but substituting Example 13A (2.00 g, 7.96 mmol) for Example 2C. Purification of the crude final product on silica gel with 5% methanol/dichloromethane provided 325 mg of the title compound. mp 141-144 °C;

¹H NMR (300 MHz, d₆-DMSO) δ 9.88 and 9.45 (br s; 1H), 8.02 and 8.33 (s; 1H), 7.90 (AB; 2H; J=7.5 Hz), 7.84 (AB; 2H; J=7.5 Hz), 7.61 (d; 2H; J=9 Hz), 7.06 (d; 2H; J=9 Hz), 4.67 (m; 0.32H), 3.92-4.25 (m; 2.68H), 1.23 and 1.18 (d; 3H; J=6 Hz); MS (DCI/NH₃) m/e 314 (M+NH₄)⁺;

- 5 Anal. calcd for C₁₇H₁₆N₂O₃: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.61; H, 5.55; N, 9.21.

Example 14

N-[2-[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]ethyl]-N-hydroxyacetamide

10

Example 14A

2-(4-(4'-Carbonitrilephenyl)phenoxy)-bromoethane

- A solution of 4-(4'-carbonitrilephenyl)phenol (3.00 g, 24.8 mmol) in DMF (20 mL) was treated with potassium carbonate (8.24 g, 99.4 mmol) and 1,2-dibromoethane (6.42 mL, 124 mmol), heated at 50 °C for 19 hours and partitioned between 3:1 ether:hexanes and water. The organic layer was separated and the aqueous layer was extracted with 3:1 ether:hexanes. The combined organic layers were dried (MgSO₄), filtered, and concentrated. Purification of the crude product on silica gel with 50% dichloromethane/hexanes) provided a white solid which was recrystallized from ether/pentane to provide 1.25 g (17%) of the title compound as colorless needles. MS (DCI/NH₃) m/e 301/303 (M)⁺, 319/321 (M+NH₄)⁺ and 336/338 (M+NH₄+NH₃)⁺.
- 15
20

Example 14B

N,O-bis(t-butyloxycarbonyl)-2-[(4-(4'-carbonitrilephenyl)phenoxy)ethyl]-N-hydroxylamine

- A solution of N,O-bis(t-butyloxycarbonyl)-N-hydroxylamine (443 mg, 1.9 mmol) in DMF (15 mL) was treated with a 60 % oil dispersion of sodium hydride (76 mg, 1.9 mmol), stirred at ambient temperature for 15 minutes, treated with Example 13A (0.54 g, 1.79 mmol), stirred for 4 hours at ambient temperature and partitioned between 1:1 ether:hexanes and saturated aqueous ammonium chloride. The organic layer was separated, and the aqueous layer was extracted with 1:1 ether:hexanes. The combined organic layers were dried (MgSO₄), filtered, and concentrated. Purification on silica gel with 10% ethyl acetate/hexanes provided 0.65 g (80%) of the title compound as colorless viscous oil. MS (DCI/NH₃) m/e 472 (M+NH₄)⁺.
- 25
30

35

Example 14C

2-[(4-(4'-Carbonitrilephenyl)phenoxy)ethyl-N-hydroxylamine hydrochloride

Example 14B (0.64 g, 1.41 mmol) was treated with 4N hydrochloric acid in dioxane (10 mL) and stirred at ambient temperature for 2.5 hours, during which time a colorless precipitate formed. The precipitate was collected by filtration, washed with dioxane, and dried to afford the HCl salt of the title compound as a colorless solid (0.22 g, 56%).

Example 14D

N,O-bis(acetyl)-2-[(4-(4'-carbonitrilephenyl)phenoxy)ethyl-N-hydroxylamine

A solution of Example 14C (27 mg, 0.093 mmol) in THF at 0 °C was treated with triethylamine (32 µL, 0.23 mmol), stirred for 1 hour at 0 °C, treated dropwise with acetyl chloride (16 µL), stirred for 1 hour at 0 °C and 18 hours at ambient temperature and partitioned between 1N aqueous hydrochloric acid and ether. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried (MgSO₄), filtered, and concentrated. Purification of the residue on silica gel with 2% acetone/dichloromethane provided 29 mg (83%) of the title compound. MS (DCI/NH₃) m/e (M+NH₄)⁺.

Example 14D

N-[2-[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]ethyl]-N-hydroxyacetamide

A solution of Example 14D (29 mg, 0.077 mmol) in THF (5 mL) and ethanol (2 mL) was cooled to 0 °C, treated with aqueous lithium hydroxide (0.31 mL of 1.0 N lithium hydroxide), stirred at 0 °C for 10 minutes and at ambient temperature for 1.5 hours and partitioned between water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with 1N aqueous hydrochloric acid, dried (MgSO₄), filtered, and concentrated to a semi-solid which was purified by trituration with ethyl acetate to provide 19.7 mg (86%) of the title compound as a colorless solid.

mp 174-175 °C;

¹H NMR (300 MHz, d₆-DMSO) δ 9.90 (br s; 1H), 7.88 (AB; 2H; J=7.5 Hz), 7.84 (AB; 2H; J=7.5 Hz), 7.71 (d; 2H; J=8.5 Hz), 7.07 (d; 2H; J=8.5 Hz), 4.20 (t; 2H; J=7.5, 7.5 Hz), 3.89 (t; 2H; J=7.5, 7.5 Hz), 2.02 (s; 3H);

MS (DCI/NH₃) m/e 297 (M+H)⁺ and 314 (M+NH₄)⁺;

Anal. calcd for C₁₇H₁₆N₂O₃(0.25H₂O): C, 67.87; H, 5.52; N, 9.31. Found: C, 67.65; H, 5.55; N, 9.12.

Example 15

N-[2-[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]ethyl]-*N*-hydroxyformamide

A solution of Example 14C (78 mg, 0.27 mmol) in THF (2.0 mL) was treated with triethylamine (75 μ L, 0.54 mmol) and then dropwise with formicacetyl anhydride (41 mg, 0.30 mmol) in THF (0.5 mL), stirred for 2 hours at ambient temperature and partitioned between ethyl acetate and 1N aqueous hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried (MgSO₄), filtered, and concentrated. Purification by chromatography on silica gel with 0.2% acetic acid/ethyl acetate and subsequent recrystallization from cold methanol provided 14.7 mg (19%) of the title compound.

mp 142-145 °C;

¹H NMR (300 MHz, d₆-DMSO) δ 10.17 and 9.74 (br s; 1H), 8.34 and 7.98 (br s; 1H), 7.88 (AB; 2H; J=7.5 Hz), 7.84 (AB; 2H; J=7.5 Hz), 7.73 (d; 2H; J=8.5 Hz), 7.07 (d; 2H; J=8.5 Hz), 4.14-4.26 (m; 2H), 3.77-3.88 (m; 2H);

MS (DCI/NH₃) m/e 300 (M+NH₄)⁺;

Anal. calcd for C₁₆H₁₄N₂O₃(0.125H₂O): C, 67.54; H, 5.05; N, 9.84. Found: C, 67.59; H, 5.32; N, 9.53.

Example 16

N-[1-[4-[(2*E*-phenylethenyl)phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

Example 16A

3-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)-2-methoxymethoxy-prop-1-ene

A mixture of 1,5,5 trimethylhydantoin (7.0 g, 49.2 mmol), powdered potassium carbonate (8.16g, 59 mmol) and 2-methoxymethoxy-allyl chloride (7.65 g, 56 mmol) in dry DMF (100 mL) was heated to 100° C with stirring for 1.5 h. The reaction mixture was cooled, filtered and the filtrate was concentrated, then partitioned between ethyl acetate and water. The organic extract was washed twice with water, brine, dried and concentrated, then purified via silica gel chromatography eluting with 50% ethyl acetate: hexane to give 10.58 g (89%) of the title compound. MS (DCI/NH₃) m/e 243 (M+H)⁺ and 260 (M+NH₄)⁺.

Example 16B

1-bromo-3-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)propan-2-one

A 0° C solution of example 16A (10.58 g, 43.7 mmol) in acetone (200 mL) was treated sequentially with a solution of potassium carbonate (0.58g, 4.2 mmol) in water (60 mL) and *N*-bromo succinimide (8.56g, 48 mmol) and the resulting mixture was stirred with

the ice bath in place. An additional 2 portions of 1.5 g of *N*-bromo succinimide were added after 1 and 2 h respectively. The ice bath was then removed and the reaction was allowed to stir for an additional 10 min, then was concentrated and extracted twice with ethyl acetate. The combined extracts were washed with aq. 0.5 M NaHSO₃, 1M NaHCO₃, water, brine, dried, filtered, and concentrated. The residue was purified via silica gel chromatography eluting with 50% ethyl acetate: hexane to give 7.39 g (61%) of the title compound.
MS (DCI/NH₃) m/e 277/279 (M+H)⁺ and 294/296 (M+NH₄)⁺.

Example 16C

1-(4'-bromophenoxy)-3-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)-2-propanone

To a suspension of 4-bromophenol (3.99g, 23.0mmol) and cesium carbonate (7.45g, 22.9mmol) in DMF (150mL) was added a solution of bromoketone 16B (3g, 11.5mmol) in DMF (5mL), drop-wise over 30 minutes. The suspension held at rt for 16h, diluted with ethyl acetate (500mL) and the organics washed with water, brine and dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (hexane/ethyl acetate 1:1) gave 2.55g of 16C as a white solid.

Example 16D

To a warm (100°) solution of 16C (0.5g, 1.35mmol) and tributyl(phenylethynyl)tin (0.64g, 1.62mmol, Aldrich) in toluene (25mL) was added a catalytic amount of Pd(PPh₃)₄. The reaction was brought to reflux and held for 7h. The resulting black solution was diluted with ethyl acetate (125mL) and the organics washed with 1M NaOH, brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (gradient elution; hexane/ethyl acetate 4:1 to 1:1) gave 0.24g of the desired compound after trituration with diethyl ether.

Example 16E

N-[1-[4-[(2*E*-phenylethenyl)phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

The title compound was prepared in the same manner as example 2D,E,F substituting 16D for 2C.

¹H NMR (300 MHz, d₆-DMSO) δ 9.90 (s, 0.5H), 9.58 (s, 0.5H), 8.31 (s, 0.5H), 7.9 (s, 0.5H), 7.57-7.54 (m, 6H), 7.38-7.33 (m, 2H), 7.26-7.08 (m, 6H), 6.94-6.90 (m, 2H), 4.80-4.60 (m, 0.5H), 4.55-4.40 (m, 0.5H), 4.16-4.04 (m, 4H), 3.76-3.73 (m, 2H), 3.61-3.57 (2, 2H), 2.79 (s, 6H), 1.28 (s, 12H);
MS (ESI) m/e M-H (436), M+H (438);

Anal. Calcd for: C₂₄H₂₇N₃O₅•H₂O: C, 63.28; H, 6.41; N, 9.22. Found: C, 63.06; H, 5.97; N, 8.94.

Example 17

N-[1-[[4-(2-furanyl)phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Prepared in the same manner as example 16 substituting 2-(tributylstannyl) furan for tributyl(phenylethynyl)tin in example 16D.

¹H NMR (300 MHz, d₆-DMSO) δ 9.86 (s, 0.5H), 9.53 (s, 0.5H), 8.30 (s, 0.5H), 7.91 (s, 0.5H), 7.67-7.61 (m, 6H), 6.96-6.94 (m, 4H), 6.79-6.74 (d, 2H, J=3.4 Hz), 6.55-6.54 (m, 2H), 4.80-4.60 (m, 0.5H), 4.45-4.30 (m, 0.5H), 4.17-3.98 (m, 6H), 3.76-3.70 (m, 2H), 3.62-3.56 (m, 2H), 2.79 (s, 6H), 1.28 (s, 12H);

MS (ESI) m/e M+H (402), M-H (400), M+NH₄ (419);

Anal. Calcd for: C₂₀H₂₃N₃O₆: C, 59.84; H, 5.77; N, 10.46. Found: C, 59.83; H, 5.90; N, 10.12.

Example 18

N-[1-[[4-(4'-butoxy[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 18A

1-(4'-butoxy-[1,1'-biphenyl]-4-yl)oxy)-3-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)-2-propanone

To a warm (75°) solution of example 16C (0.1g, 0.27mmol) and 4-butoxyphenylboronic acid (0.08g, 0.41mmol) in DME (2mL) was added a 1M Na₂CO₃ solution (0.4mL) followed by a catalytic amount of PdCl₂(dppf). The reaction was held at 100° for 2h, diluted with ethyl acetate (25mL), washed with sat'd ammonium chloride, water, brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (20% ethyl acetate in methylene chloride) gave 0.105g of **5** as a white solid.

Example 18B

N-[1-[[4-(4'-butoxy[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Prepared in the same manner as example 2D,E,F substituting 18A for 2C.

¹H NMR (300 MHz, d₆-DMSO) δ 9.87 (s, 0.5H), 9.55 (s, 0.5H), 8.31 (s, 0.5H), 7.91 (s, 0.5H), 7.55-7.50 (m, 8H), 6.98-6.95 (m, 8H), 4.80-4.60 (m, 0.5H), 4.50-4.35 (m, 0.5H),

4.16-4.06 (m, 4H), 4.01-3.96 (t, 4H, J=7.0, 5.9 Hz), 3.76-3.70 (m, 2H), 3.62-3.59 (m, 2H), 2.80 (s, 6H), 1.72-1.65 (m, 4H), 1.48-1.40 (m, 4H), 1.29 (s, 12H), 0.96-0.91 (t, 6H, J=7.1, 7.5 Hz);

MS (ESI) m/e M+H (484), M+NH₄ (506);

- 5 Anal. Calcd for: C₂₆H₃₃N₃O₆: C, 64.57; H, 6.87; N, 8.68. Found: C, 64.70; H, 7.04; N, 8.50.

Example 19

10 N-[1-[[[(4'-fluoro[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 19A

3-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)-propan-[1,2]oxirane

- 15 The title compound was prepared following the procedures described for example 5A and 5C, but using allyl alcohol in place of 3-buten-1-ol.

Example 19B

20 N-[1-[[[(4'-fluoro[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

- Prepared according to the sequence of reaction described in examples 5D through 5H, substituting 19A for 5C in example 5D and 4-(4'-fluorophenyl)-phenol for 4'-hydroxy-4-biphenyl carbonitrile in example 5F.
1H NMR (300 MHz, d₆-DMSO) δ 9.86 (s, 0.5H), 9.54 (s, 0.5H), 8.31 (s, 0.5H), 7.91 (s, 0.5H), 7.67-7.57 (m, 6H), 7.27-7.22 (m, 3H), 7.01-6.97 (m, 3H), 4.96-4.70 (m, 0.5H),
25 4.50-4.40 (m, 0.5H), 4.18-4.08 (m, 3H), 3.77-3.73 (m, 2H), 2.79 (s, 6H), 1.28 (s, 12H).
MS (ESI) m/e 430 (M+H), 428 (M-H);
Anal. Calcd for: C₂₂H₂₄N₃O₅F•0.5H₂O: C, 60.26; H, 5.74; N, 9.58. Found: C, 60.48; H, 5.66; N, 8.72.

Example 20

30 N-[1-[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy]ethyl]-N-hydroxyformamide

- Prepared according to the sequence of reaction described in examples 5D through 5H, substituting 19A for 5C in example 5D and substituting 4-(4'-
35 Trifluoromethylphenyl)phenol for 4'-hydroxy-4-biphenyl carbonitrile in example 5F.
1H NMR (300 MHz, d₆-DMSO) δ 9.80 (s, 0.5H), 9.58 (s, 0.5H), 8.32 (s, 0.5H), 7.92 (s, 0.5H), 7.87-7.84 (d, 4H, J=8.1 Hz), 7.79-7.76 (d, 4H, J=8.8 Hz), 7.72-7.69 (d, 4H, J=8.4

Hz), 7.06-7.02 (m, 4H), 4.80-4.60 (m, 0.5H), 4.45-4.40 (m, 0.5H), 4.20-4.12 (m, 4H), 3.78-3.74 (m, 2H), 3.63-3.62 (m, 2H), 2.08 (s, 6H), 1.30 (s, 12H);
MS (ESI) m/e M-H (478), M+H (480);
Anal. Calcd for: C₂₃H₂₄N₃O₅F₃•0.5H₂O: C, 56.55; H, 5.15; N, 8.60. Found: C, 56.52;
H, 5.07; N, 8.43.

Example 21

N-[1-[[[4'-methoxy[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Prepared according to the sequence of reaction described in examples 5D through 5H, substituting 19A for 5C in example 5D and substituting 4-(4'-methoxyphenyl)phenol for 4'-hydroxy-4-biphenyl carbonitrile in example 5F.

¹H NMR (300 MHz, d₆-DMSO) δ 9.89 (s, 0.5H), 9.57 (s, 0.5H), 8.31 (s, 0.5H), 7.91 (s, 0.5H), 7.56-7.53 (d, 8H, J=8.8 Hz), 7.01-6.94 (m, 8H), 4.80-4.60 (m, 0.5H), 4.44-4.35 (m, 0.5H), 4.17-3.95 (m, 4H), 3.74-3.71 (m, 2H), 3.63-3.58 (m, 2H), 2.79 (s, 6H), 1.28 (s, 12H);

MS (ESI) m/e M+H (442);

Anal. Calcd for: C₂₃H₂₆N₃O₆•0.25H₂O: C, 62.08; H, 6.00; N, 9.44. Found: C, 62.25; H, 6.30; N, 8.94.

Example 22

N-[1-[[[4'-methyl[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Prepared according to the sequence of reaction described in examples 5D through 5H, substituting 19A for 5C in example 5D and substituting 4-(4'-methylphenyl)phenol for 4'-hydroxy-4-biphenyl carbonitrile in example 5F.

¹H NMR (300 MHz, d₆-DMSO) δ 9.89 (s, 0.5H), 9.57 (s, 0.5H), 8.31 (s, 0.5H), 7.92 (s, 0.5H), 7.59-7.56 (d, 4H, J=8.8 Hz), 7.52-7.49 (d, 4H, J=8.1 Hz), 7.24-7.22 (d, 4H, J=7.7 Hz), 7.00-6.97 (m, 4H), 4.80-4.60 (m, 0.5H), 4.40-4.35 (m, 0.5H), 4.40-4.1 (m, 4H), 3.80-3.55 (m, 2H), 3.60-3.50 (m, 2H), 2.79 (s, 6H), 2.32 (s, 6H), 1.28 (s, 12H);

MS (ESI) m/e 424 (M-H), 426 (M+H);

Anal. Calcd for: C₂₃H₂₇N₃O₅•0.25H₂O: C, 64.24; H, 6.44; N, 9.77. Found: C, 64.30; H, 6.55; N, 9.36.

Example 23

N-[1-[[[4'-butoxy[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 23A

1-bromo-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)propan-2-one

The title compound was prepared following the procedure described in examples

- 5 16A and 16 B, except substituting 5,5 dimethylhydantoin for 1,5,5 trimethylhydantoin in example 16A.

Example 23B

N-[1-[[[4'-butoxy[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

10

Prepared according to the procedures of example 16C and 16E, substituting example 23A for 16B and 4-(4'-Butyloxyphenyl)phenol for 4-bromophenol in example 16C.

- 15 ¹H NMR (300 MHz, d₆-DMSO) δ 9.86 (s, 0.5H), 9.55 (s, 0.5H), 8.36 (s, 0.5H), 8.34 (s, 0.5H), 8.32 (s, 0.5H), 7.94 (s, 0.5H), 7.55-7.51 (m, 8H), 6.99-6.96 (m, 8H), 4.85-4.80 (m, 0.5H), 4.40-4.36 (m, 0.5H), 4.20-4.06 (m, 2H), 4.01-3.97 (m, 4H), 3.78-3.71 (m, 2H), 3.60-3.51 (m, 2H), 1.73-1.66 (m, 6H), 1.48-1.38 (m, 4H), 1.25 (s, 12H), 0.96-0.86 (m, 6H);

MS (ESI) m/e M-H (468);

- 20 Anal. Calcd for: C₂₅H₃₀N₃O₆: C, 63.95; H, 6.65; N, 8.94. Found: C, 63.89; H, 6.91; N, 8.63.

Example 24

N-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[(4'-ethoxy[1,1'-biphenyl]-4-yl)oxy]ethyl]-N-hydroxyformamide

25

Prepared according to the procedures of example 23B, except substituting 4-(4'-ethoxyphenyl)phenol for 4-(4'-Butyloxyphenyl)phenol.

- 30 ¹H NMR (300 MHz, d₆-DMSO) δ 9.84 (s, 0.5H), 9.52 (s, 0.5H), 8.37 (s, 0.5H), 8.32 (s, 2H), 7.92 (s, 0.5H), 7.55-7.52 (m, 8H), 6.98-6.95 (d, 4H, J=8.8 Hz), 4.90-4.80 (m, 0.5H), 4.45-4.30 (m, 0.5H), 4.19-3.98 (m, 8H), 3.74-3.67 (m, 2H), 3.59-3.53 (m, 2H), 1.36-1.25 (m, 18H);

MS (ESI) m/e M-H (440), M+H (442);

Anal. Calcd for: C₂₃H₂₇N₃O₆•0.5H₂O: C, 61.32; H, 6.26; N, 9.32. Found: C, 61.12; H, 6.35; N, 9.32.

35

Example 25

N-[1-[[4-(1,3-benzodioxol-5-yl)phenoxy]methyl]-2-(4,4-dimethy-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

Prepared according to the procedures of example 23B, except substituting 4-(3',4'-methylenedioxyphenyl)-phenol for 4-(4'-Butyloxyphenyl)phenol.

- 5 ¹H NMR (300 MHz, d₆-DMSO) δ 9.84 (s, 0.5H), 9.52 (s, 0.5H), 8.37-8.31 (m, 3H), 7.91 (s, 0.5H), 7.55-7.52 (d, 4H, J=8.5 Hz), 7.19 (s, 2H), 7.09-7.06 (m, 2H), 6.97-6.93 (d, 6H, J=10.2 Hz), 6.03 (s, 4H), 4.70-4.60 (m, 0.5H), 4.45-4.30 (m, 0.5H), 4.16-3.96 (s, 6H), 3.73-3.57 (m, 5H), 1.27 (s, 12H);
- MS (ESI) m/e M+H (442), M-H (440);
- 10 Anal. Calcd for: C₂₂H₂₃N₃O₇•0.50H₂O: C, 58.66; H, 5.37; N, 9.32. Found: C, 58.70; H, 5.80; N, 8.79.

Example 26

N-[1-[[4-(4'-butoxy[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3-methy-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

15

Example 26A

1-bromo-3-(3-methyl-2,5-dioxoimidazolidin-1-yl)propan-2-one

The title compound was prepared following the procedure described in examples 20 16A and 16 B, except substituting 1-methylhydantoin for 1,5,5 trimethylhydantoin in example 16A.

Example 26B

N-[1-[[4-(4'-butoxy[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3-methy-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

25

Prepared according to the procedures of example 16C and 16E, substituting example 26A for 16B and 4-(4'-Butyloxyphenyl)phenol for 4-bromophenol in example 16C.

- 30 ¹H NMR (300 MHz, d₆-DMSO) δ 9.97 (s, 0.5H), 9.60 (s, 0.5H), 8.34 (s, 0.5H), 7.97 (s, 0.5H), 7.55-7.50 (m, 8H), 6.99-6.91 (m, 8H), 4.86-4.82 (m, 0.5H), 4.33-4.31 (m, 0.5H), 4.18-4.12 (m, 2H), 3.99-3.94 (m, 4H), 2.85 (s, 6H), 1.82-1.68 (m, 4H), 1.50-1.38 (m, 6H), 0.96-0.91 (m, 6H);
- MS (ESI) m/e M-H (454);
- 35 Anal. Calcd for: C₂₄H₂₉N₃O₆•0.25C₄H₅O: C, 63.51; H, 6.44; N, 8.88. Found: C, 63.59; H, 6.46; N, 8.68.

Example 27

N-[1-[[[4-(3-thienyl)phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting 4-(4'-(3-thienyl)phenyl)phenol for 4-bromophenol in example 16C.

- 5 ¹H NMR (300 MHz, d₆-DMSO) δ 9.90 (s, 0.5H), 9.57 (s, 0.5H), 8.31 (s, 0.5H), 7.91 (s, 0.5H), 7.75-7.74 (m, 2H), 7.67-7.60 (m, 6H), 7.52-7.49 (m, 2H), 6.96-6.92 (m, 4H), 4.80-4.6 (m, 0.5H), 4.50-4.4 (m, 0.5H), 4.19-3.98 (m, 6H), 3.81-3.70 (m, 2H), 3.61-3.56 (m, 2H), 2.79 (s, 6H), 1.29 (s, 12H);
- Anal. Calcd for: C₂₀H₂₃N₃O₅S: C, 57.54; H, 5.55; N, 10.06. Found: C, 57.72; H, 5.84;
- 10 N, 9.76.

Example 28

N-[1-[[[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting 4-phenyl-phenol for 4-bromophenol in example 16C.

- 15 ¹H NMR (300 MHz, d₆-DMSO) δ 9.90 (S, 0.5H), 9.57 (S, 0.5H), 8.30 (S, 0.5H), 7.92 (S, 0.5H), 7.62-7.60 (D, 8H, J=8.1 Hz), 7.45-7.40 (t, 4H, J=5.8, 7.8 Hz), 7.33-7.28 (t, 2H, J=7.1, 6.9 Hz), 7.02-6.97 (m, 4H), 4.80-4.60 (m, 0.5H), 4.45-4.40 (m, 0.5H), 4.18-4.01 (m, 20 4H), 3.77-3.70 (m, 2H), 3.63-3.6 (m, 2H), 2.80 (s, 6H), 1.28 (s, 12H);
- MS (ESI) m/e M-H (410), M+H (412);
- Anal. Calcd for: C₂₂H₂₅N₃O₅•0.25H₂O: C, 63.25; H, 6.17; N, 10.10. Found: C, 63.94; H, 6.41; N, 9.60.

Example 29

N-[1-[[[3'-chloro-4'-fluoro[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting 4-(4'-fluoro-3'-chloro-phenyl)phenol for 4-bromophenol in example 16C.

- 30 ¹H NMR (300 MHz, d₆-DMSO) δ 9.90 (s, 0.5H), 9.57 (s, 0.5H), 8.31 (s, 0.5H), 7.92 (s, 0.5H), 7.84-7.82 (m, 2H), 7.65-7.61 (m, 6H), 7.49-7.43 (t, 2H, J=9.2, 8.8 Hz), 7.02-6.96 (m, 4H), 4.80-4.60 (m, 0.5H), 4.43-4.40 (m, 0.5H), 4.21-4.06 (m, 4H), 3.82-3.70 (m, 2H), 3.62-3.59 (m, 2H), 2.79 (s, 6H), 1.28 (s, 12H);
- MS (ESI) m/e M-H (462), M+H (464);
- 35 Anal. Calcd for: C₂₂H₂₃N₃O₅ClF•0.25H₂O: C, 56.41; H, 5.05; N, 8.97. Found: C, 56.78; H, 5.24; N, 8.55.

Example 30

N-[1-[[[(2'-methyl[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethoxy-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting 4-(3'-methyl-phenyl)phenol for 4-bromophenol in example 16C.

¹H NMR (300 MHz, d₆-DMSO) δ 9.90 (s, 0.5H), 9.57 (s, 0.5H), 8.32 (s, 0.5H), 7.93 (s, 0.5H), 7.28-7.14 (m, 12H), 6.99-6.64 (m, 4H), 4.90-4.80 (m, 0.5H), 4.42-4.40 (m, 0.5H), 4.22-4.04 (m, 6H), 3.82-3.74 (m, 2H), 3.62-3.58 (m, 2H), 2.80 (s, 6H), 2.20 (s, 6H), 1.29 (s, 12H);

MS (ESI) m/e M+H (426), M-H (424);

Anal. Calcd for: C₂₃H₂₇N₃O₅•0.25H₂O: C, 64.24; H, 6.44; N, 9.77. Found: C, 64.50; H, 6.69; N, 9.31.

Example 31

N-[1-[[[(4'-cyanol[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

Example 31A

3-(4-(4'-Carbonitrilephenyl)phenoxy)-1-bromopropan-2-one

The title compound was prepared according to the procedure described in examples 16A and 16B, but substituting 4-(4'-cyanophenyl)-phenol for 1,5,5-trimethyl hydantoin in example 16A.

Example 31B

N-[1-[[[(4'-cyanol[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting example 31A for 16B and hydantoin for 4-bromophenol in example 16C.

¹H NMR (300 MHz, DMSO-d₆) δ 3.6-3.8 (m, 2H), 3.92 (d, 2H, J=8.4 Hz), 4.10-4.25 (m, 2H), 4.3-4.4 (m, 0.5H), 4.8-4.9 (m, 0.5H), 7.0-7.1 (m, 2H), 7.74 (d, 2H, J=9.0 Hz), 7.84 (d, 2H, J=8.4 Hz), 7.89 (d, 2H, J=8.4 Hz), 7.98 (s, 0.5H), 8.1-8.2 (m, 1H), 8.35 (s, 0.5H), 9.57 (br s, 0.5H), 9.53 (br s, 0.5H);

MS (ESI+) 395 (M+H);

Anal. Calcd for C₂₀H₁₈N₄O₅•0.2H₂O•0.4EtOAc: C, 59.88; H, 5.03; N, 12.93. Found: C, 59.80; H, 4.81; N, 12.74.

Example 32

N-[1-[(4'-cyanol[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)ethyl]-N-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting example 31A for 16B and saccharin for 4-bromophenol in example 16C.

¹H NMR (300 MHz, DMSO-d₆) δ 3.9-4.2 (m, 2H), 4.2-4.3 (m, 2H), 4.45-4.55 (m, 0.5H), 5.0-5.1 (m, 0.5H), 7.0-7.1 (m, 2H), 7.74 (d, 2H, J=8.4 Hz), 7.85 (d, 2H, J=8.7 Hz), 7.88 (d, 2H, J=8.4 Hz), 8.0-8.2 (m, 3.5H), 8.3-8.4 (m, 1.5H), 9.78 (s, 0.5H), 10.14 (s, 0.5H). MS (ESI-) 476 (M-H);

Anal. Calcd for C₂₄H₁₉N₃O₆S•1.1H₂O: C, 57.97; H, 4.30; N, 8.45. Found: C, 58.01; H, 3.96; N, 8.16.

Example 33

N-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-N-hydroxyformamide

Prepared according to the procedures of example 23B, except substituting 4-(4'-trifluoromethoxy phenyl)-phenol for 4-(4'-Butyloxyphenyl)-phenol.

¹H NMR (300 MHz, DMSO-d₆) δ 1.27 (s, 6H), 3.5-3.8 (m, 2H), 4.0-4.3 (m, 2H), 4.4-4.5 (m, 0.5H), 4.8-4.9 (m, 0.5H), 7.0-7.2 (m, 2H), 7.42 (d, 2H, J=7.8 Hz), 7.64 (d, 2H, J=8.4 Hz), 7.75 (d, 2H, J=8.7 Hz), 7.93 (s, 0.5H), 8.33 (s, 0.5H), 8.35 (s, 0.5H), 8.40 (s, 0.5H), 9.56 (s, 0.5H), 9.87 (s, 0.5H);

MS (ESI+) 482 (M+H);

Anal. Calcd for C₂₂H₂₁N₃O₆F₃: C, 54.88; H, 4.60; N, 8.72. Found: C, 55.22; H, 4.87; N, 8.36.

Example 34

N-[1-[[4-(4-phenyl-1-piperidinyl)phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting the 4-phenyl-N-phenyl piperidine (prepared as in Warner-Lambert patent WO 97/19068), for 4-bromophenol in example 16C.

¹H NMR (300 MHz, DMSO-d₆) δ 1.27 (s, 3H), 1.28 (s, 3H), 1.7-1.9 (m, 4H), 2.55-2.75 (m, 3H), 2.78 (s, 1.5H), 2.79 (s, 1.5H), 3.5-3.8 (m, 4H), 3.9-4.1 (m, 2H), 4.3-4.4 (m, 0.5H), 4.7-4.8 (m, 0.5H), 6.81 (d, 2H, J=8.7Hz), 6.93 (d, 2H, J=9.0 Hz), 7.15-7.25 (m, 1H), 7.25-7.35 (m, 4H), 7.89 (s, 0.5H), 8.30 (s, 0.5H), 9.54 (s, 0.5H), 9.86 (s, 0.5H);

MS (ESI+) 495 (M+H);

Anal. Calcd for C₂₇H₃₄N₄O₅: C, 65.56; H, 6.92; N, 11.32. Found: C, 65.35; H, 7.24; N, 10.93.

Example 35

N-[1-[(4,4-dimethy-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy]ethyl]-*N*-hydroxyformamide

Prepared according to the procedures of example 23B, except substituting 4-(4'-trifluoromethylphenyl)phenol for 4-(4'-Butyloxyphenyl)phenol .

¹H NMR (300 MHz, DMSO-d₆) δ 1.28 (s, 6H), 3.5-3.8 (m, 2H), 4.1-4.3 (m, 2H), 4.4-4.5 (m, 0.5H), 4.8-4.9 (m, 0.5H), 7.0-7.2 (m, 2H), 7.72 (d, 2H, J=8.4 Hz), 7.78 (d, 2H, J=8.4 Hz), 7.86 (d, 2H, J=8.4 Hz), 7.93 (s, 0.5H), 8.33 (s, 0.5H), 8.35 (s, 0.5H), 8.40 (s, 0.5H), 9.56 (s, 0.5H), 9.87 (s, 0.5H);

MS (ESI+) 466 (M+H);

Anal. Calcd for C₂₂H₂₂N₃O₅F₃•0.6H₂O: C, 55.49; H, 4.91; N, 8.82. Found: C, 55.55; H, 4.66; N, 8.77.

Example 36

N-[1-[(3'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-[methyl]-(4-methylphenyl)sulfonyl]amino]ethyl]-*N*-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting example 31A for 16B and *N*-methyl-(p-tolyl)sulfonamide for 4-bromophenol in example 16C.

¹H NMR (300 MHz, DMSO-d₆) δ 2.41 (s, 3H), 2.70 (s, 1.5H), 2.73 (s, 1.5H), 3.05-3.35 (m, 2H), 4.0-4.2 (m, 2H), 4.3-4.4 (m, 0.5H), 4.8-4.9 (m, 0.5H), 7.06 (d, 2H, J=8.7 Hz), 7.46 (d, 2H, J=8.1 Hz), 7.65-7.8 (m, 4H), 7.85 (d, 2H, J=8.7 Hz), 7.89 (d, 2H, J=8.7 Hz), 8.04 (s, 0.5H), 8.40 (s, 0.5H), 9.71 (s, 0.5H), 10.0 (s, 0.5H);

MS (ESI+) 480 (M+H);

Anal. Calcd for C₂₅H₂₅N₃O₅S: C, 62.61; H, 5.25; N, 8.76. Found: C, 62.52; H, 5.27; N, 7.98.

Example 37

N-[1-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-[4,4-dimethy-2,5-dioxo-3-(3-pyridinylmethyl)-1-imidazolidinyl]ethyl]-*N*-hydroxyformamide

Example 37A

3-(3-pyridinylmethyl))-2,5-dioxo-4,4-dimethylimidazolidine

The title compound was prepared following the procedures described in examples 68A, 68B and 69B, except substituting 3-picolyl chloride for methyl iodide in example 68B.

Example 37B

N-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-[4,4-dimethoxy-2,5-dioxo-3-(3-pyridinyl)methyl]-1-imidazolidinyl]ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 16C and 16E, substituting example 31A for 16B and 37A for 4-bromophenol in example 16C.

¹H NMR (300 MHz, DMSO-d₆) δ 1.25 (s, 6H), 3.6-3.7 (m, 1H), 3.8-3.9 (m, 1H), 4.1-4.3 (m, 2H), 4.4-4.5 (m, 0.5H), 4.56 (s, 2H), 4.85-4.95 (m, 0.5H), 7.0-7.1 (m, 2H), 7.35 (dd, 1H, J=8.1,4.8 Hz), 7.7-7.8 (m, 3H), 7.86 (d, 2H, J=8.4 Hz), 7.90 (d, 2H, J=8.4 Hz), 7.96 (s, 0.5H), 8.34 (s, 0.5H), 8.45-8.50 (narrow m, 1H), 8.60 (s, 1H), 9.64 (s, 0.5H), 9.97 (s, 0.5H);

MS (ESI (+)) 514 (M+H);

Anal. Calcd for C₂₈H₂₇N₅O₅•1.7H₂O: C, 61.80; H, 5.63; N, 12.87. Found: C, 61.77; H, 5.08; N, 12.48.

Example 38

N-[2-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]-1-methylpropyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 16C and 16E, substituting 3-bromo-2-butanone for 16B and 4-(4'-cyanophenyl)phenol for 4-bromophenol in example 16C.

¹H NMR (300 MHz, DMSO-d₆) δ 1.1-1.3 (m, 6H), 3.8-4.0 (m, 1H), 4.3-4.7 (m, 1H), 7.0-7.1 (m, 2H), 7.6-7.7 (m, 2H), 7.8-7.9 (m, 4H), 8.02 (s, 0.5H), 8.28 (s, 0.25H), 8.33 (s, 0.25H), 9.43 (s, 0.25H), 9.60 (s, 0.25H), 9.85 (s, 0.25H), 9.95 (s, 0.25H). MS (ESI+) 311 (M+H). Anal. Calcd for C₁₈H₁₈N₂O₃•0.2H₂O: C, 68.86; H, 5.91; N, 8.92. Found: C, 68.73; H, 5.79; N, 8.58.

Example 39

N-[1-[[[(3'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 39A

3'-cyano-4-hydroxy biphenyl

A 250 mL flask was charged with 2.21g (2.7 mmol) [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium (II) • CH₂Cl₂ and 6.26g (2.73 mmol) 3-iodobenzonitrile, 6.0g (3.95 mmol) 4-methoxyphenylboronic acid and 12.45g (8.20 mmol) cesium fluoride added as solids followed by addition of 180 mL 1,2-dimethoxyethane. The flask was flushed with N₂ and the suspension heated to reflux which was maintained for 3 hours. the cooled

reaction mixture was filtered through a pad of 300g flash silica gel and the pad was washed with 1L ethyl acetate. The ethyl acetate was concentrated and the residue purified by flash chromatography eluting with 10% hexanes/ 90% ethyl acetate to give 3.3g of the desired product (58% yield). This material was dissolved in 50 mL anhydrous CH₂Cl₂ and the solution cooled in a dry ice- acetone bath and a solution of boron tribromide (40 mL, 4 mmol) was added dropwise under inert atmosphere. The reaction solution was then stirred at room temperature overnight. The reaction solution was cooled in an ice bath and 5 mL of H₂O added dropwise followed by the addition of 20 mL 1N HCl. The mixture was stirred for 1 hour and the resulting suspension was filtered and the filtrate transferred to a separatory funnel and the organic layer separated off and set aside. the filtered solid was washed with H₂O and ethyl acetate and filtered and the filtrate transferred to the separatory funnel and the organic layer combined with the previous organic layer, dried over Na₂SO₄, filtered and the filtrate concentrated to a 3.05g of a white solid (99% yield).

Example 39B

N-[1-[[[(3'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting 3'-cyano-4-hydroxy biphenyl for 4-bromophenol in example 16C.
mp: 130-132 °C;

¹H NMR (DMSO- δ 6) δ 9.86 (s, 1/2H), 9.48-9.63 (c, 1/2H), 8.33 (s, 1/2H), 8.09 (s, 1H), 7.97 (d, 1H, J=4.5 Hz), 7.93 (s, 1/2H), 7.75 (d, 1H, J=4.5 Hz), 7.70 (d, 2H, J=6.0 Hz), 7.63 (t, 1H, J=4.5 Hz), 7.00-7.07 (c, 2H), 4.83-4.90 (c, 1/2H), 4.60-4.67 (c, 1/2H);

ESI(+): 409 (M-27), 437 (M+H), 454 (M+NH₄), 459 (M+Na);

Anal. Calcd for: C₂₃H₂₄N₄O₅•0.25C₄H₈O₂: C, 62.87; H, 5.71; N, 12.21. Found: C, 62.68; H, 5.55; N, 12.27.

Example 40

N-[1-[[[4'-(methylthio)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting 4'-thiomethyl-4-hydroxy biphenyl for 4-bromophenol in example 16C.
mp172-174.

¹H NMR (DMSO- δ 6) δ 9.48-9.96 (BS, 1H), 8.34 (S, 1/2H), 7.94 (S, 1/2H), 7.54-7.63 (C, 4H), 7.29-7.34 (C, 2H), 6.97-7.03 (C, 2H), 4.82-4.92 (C, 1/2H), 4.39-4.47 (C, 1/2H), 4.07-4.25 (C, 2H), 3.73-3.85 (C, 1H), 3.59-3.68 (C, 1H), 2.80 (S, 1.5H), 2.79 (S, 1.5H)

MS (ESI(-)) 456 ((M-H)), 913 ((2M-H)) Calcd: 458.175 Found: 458.1747;
Anal. Calcd for: C₂₃H₂₇N₃O₃S C, 60.37; H, 5.95; N, 9.19; S, 7.01 Found: C, 60.29; H, 5.82;
N, 9.08; S, 6.98.

Example 41

N-[1-[4-[[4-(trifluoromethyl)phenoxy]phenoxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting 4-(4'-trifluoromethylphenoxy)phenol for 4-bromophenol in example 16C.

mp 121-123

¹H NMR (DMSO-*d*₆) δ 9.46-9.97 (C, 1H), 8.33 (S, 1/2H), 7.94 (S, 1/2H), 7.71 (S, 1H), 7.69 (S, 1H), 7.04-7.14 (C, 4H), 6.97-7.03 (C, 2H), 4.81-4.91 (C, 1/2H), 4.39-4.47 (C, 1/2H), 4.14-4.22 (C, 1H), 4.04-4.13 (C, 1H), 2.81 (S, 1.5H), 2.80 (S, 1.5H), 1.30 (S, 1.5H);

MS (ESI(-)) 494 (M-H), 530 (M+Cl), 989 (2M-H), 1011 (2M+Na2H) Calcd: 496.169, Found: 496.1696;

Anal. Calcd for: C₂₃H₂₄F₃N₃O₆ Theory: C, 55.75; H, 4.88; N, 8.48; F, 11.50. Found: C, 55.68; H, 4.92; N, 8.40; F, 11.24.

Example 42

N-[1-[[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-2-N-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting 4'-trifluoromethoxy-4-hydroxy biphenyl for 4-bromophenol in example 16C.

mp 129.3-130 °C;

¹H NMR, 400Mz (DMSO-*d*₆): δ 9.46-9.84 (c, 1H), 8.26 (s, 1/2H), 7.87 (s, 1/2H), 7.67 (s, 1H), 7.65 (s, 1H), 7.57 (s, 1H), 7.55 (s, 1H), 7.34 (s, 1H), 7.32 (s, 1H), 6.94-6.97 (c, 2H), 4.78-4.82 (c, 1/2H), 4.34-4.38 (c, 1/2H), 4.02-4.17 (c, 2H), 3.67-3.77 (c, 1H), 3.53-3.60 (c, 1H), 2.73 (s, 1.5H), 2.72 (s, 1.5H), 1.22 (s, 3H), 1.21 (s, 3H);

MS (ESI(-)): 494 (M-H), 530 (M+Cl), 989 (2M-H), 1011 (2M+Na-2H) Calcd.: 496.1695 Found: 496.1680;

Anal. Calcd. for C₂₃H₂₄F₃N₃O₆ Theory: C, 55.75; H, 4.88; N, 8.48; F, 11.50. Found: C, 55.69; H, 4.94; N, 8.23; F, 11.71.

Example 43

N-[1-[[[4'-(methylsulfonyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Prepared according to the procedures of example 48A, 48B and 48C, substituting 16B for 23A for 4-bromophenol in example 48A.

mp 174-175 °C;

¹H NMR, 400 MHz (DMSO-d₆): δ 9.47-9.98 (c, 1H), 8.35 (s, 1/2H), 7.92-8.00 (c, 4.5H), 7.77 (s, 1H), 7.75 (s, 1H), 7.07-7.10 (c, 2H), 4.85-4.94 (c, 1/2H), 4.42-4.50 (1/2H), 4.13-4.30 (c, 2H), 3.76-3.86 (c, 1H), 3.63-3.69 (c, 1H), 3.39 (s, 3H), 2.83 (s, 1.5H), 2.82 (s, 1.5H), 1.32 (s, 3H), 1.31 (s, 3H);

MS [ESI(-)]: 488(M-H), 977(2M-H), 999(2M+Na-2H)

[ESI(+)]: 490 (M+H), 507 (M+NH₄), 512 (M+Na);

Anal. calcd. for C₂₃H₂₈.5N₃O₇.75S: Theory: C,54.91; H,5.71; N,8.35;S,6.37 Found: C,54.85; H,5.76; N,8.00; S,6.31.

Example 44

N-[1-[[[3'-(cyanomethyl)-4'-methoxy]l[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Prepared according to the procedures of example 16C and 16E, substituting 4-(3'-cyanomethyl-4'-methoxyphenyl)phenol for 4-bromophenol in example 16C.

¹H NMR (300 MHz, DMSO-d₆) δ : 1.275, 1.290 (6H), 2.788, 2.800 (3H), 3.566-3.641 (m, 1H), 3.708-3.821 (m, 1H), 4.047-4.214 (m, 2H), 4.399-4.416 (m, 0.5H), 4.846 (m, 0.5H), 6.973-7.013 (2H), 7.110-7.140 (1H), 7.543-7.608 (m, 4H), 7.291 (s, 0.5H), 8.319 (s, 0.5H), 9.576 (s, 0.5H), 9.904 (s, 0.5H);

MS (ESI) m/e 481 (M+H)⁺, 498 (M+NH₄)⁺, 479 (M-H)⁻;

Anal. calcd for C₂₅H₂₈N₄O₆.0.5MeOH: C, 61.68; H, 6.08; N, 11.28. Found: C, 62.07; H, 6.21; N, 10.91.

Example 45

N-[1-[[[3'-(cyanomethyl)l[1,1'-biphenyl]-4-yl]oxy]methyl]-3-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)propyl]-N-hydroxyformamide

The title compounds was prepared according to the procedures of example 5, except avoiding the methylation step in example 5B and substituting 4-(3'-cyanomethylphenyl)phenol for 4'-hydroxy-4-biphenylcarbonitrile in example 5F.

¹H NMR (300 MHz, DMSO-d₆) δ 1.27 (s, 6H), 1.70-2.00 (m, 2H), 3.37-3.47 (m, 2H), 3.96-4.08 (s+m, 5H), 7.00-7.03 (d, 2H, 8.4Hz), 7.28--7.31 (d, 1H, 8.7Hz), 7.426-7.477 (t, 1H, 7.5Hz), 7.56-7.61 (m, 4H), 7.915 (s, 0.73H), 8.28-8.34 (1.27H), 9.55 (s, 0.75H), 9.96 (s, 0.25H);

MS (ESI) m/e 451 (M+H)⁺, 468 (M+NH₄)⁺, 449 (M-H)⁻;

Anal. calcd for C₂₅H₂₈N₄O₆·MeOH: C, 62.22; H, 6.26; N, 11.61. Found: C, 62.25; H, 5.95; N, 11.57.

Example 46

5 N-[1-[(4'-butoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 46A

1-(4-bromophenylthio)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-propanone

10 A solution of 4-bromothiophenol (2.15 g, 11.4 mmol) in DMF (50 mL) at ambient temperature was treated with cesium carbonate (5.57 g, 17.1 mmol) for 20 minutes, treated in a single portion with example 23A (2.5 g, 9.5 mmol), stirred for 1 hours at ambient temperature and diluted with water, extracted with ethyl acetate, the combined extracts were washed with water and brine, dried (Na₂SO₄), filtered, concentrated and
15 purified on silica gel with 20 to 35 to 50% ethyl acetate/hexane to provide 3.17 g (90%) of the titled compound as a white solid.
MS (APCI) m/e 371, 373 (M+H)⁺, 388, 390 (M+NH₄)⁺, 369, 371 (M-H), 405, 407 (M+Cl)⁻.

Example 46B

20 1-[(4'-butoxy[1,1'-biphenyl]-4-yl)thio]-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-propanone

A solution of example 46A (700 mg, 1.89 mmol) in DME (20 mL) at ambient temperature was treated with 4-n-butoxybenzeneboronic acid (549 mg, 2.83 mmol),
25 tetrakis-(triphenylphosphine)-palladium (218 mg, 0.189 mmol) and 1M sodium carbonate (3.54 mL, 3.54 mmol), the reaction vessel was sealed and heated at 90°C for 6 hours, diluted with ethyl acetate, washed with sequentially saturated ammonium chloride solution, water and brine, dried (Na₂SO₄), filtered, concentrated and purified on silica gel with 30 to 50% ethyl acetate/dichloromethane to provide 650 mg (78%) of the title
30 compound as a yellow solid.
MS (APCI) m/e 441 (M+H)⁺, 458 (M+NH₄)⁺, 439 (M-H), 475 (M+Cl)⁻.

Example 46C

35 N-[1-[(4'-butoxy[1,1'-biphenyl]-4-yl)thio]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared from 46B following the procedures described in example 2D, 2E, 2F.

¹H NMR (300 MHz, DMSO-d₆) δ ; 0.919-0.967 (t, 3H, J=7.2Hz), 1.225-1.237(s+s, 6H), 1.389-1.512(m, 2H), 1.666-1.760(m, 2H), 3.110-3.192(m, 2H), 3.528-3.735 (m, 2H), 3.987-4.030(t, 2H, J=6.3Hz), 4.030(m, 0.5H), 4.750(m, 0.5H), 6.991-7.020 (d, 2H, J=9 Hz), 7.383-7.417 (dd, 2H, J=1.8, 8.4 Hz), 7.561-7.601 (4H), (1.5H), 9.56 (s, 7.767(s, 0.5H), 8.299(s, 1H), 8.337(s, 0.5H), 9.457(br s, 0.5H), 9.695(br s, 0.5H); MS (ESI) m/e 484 (M-H)⁻;

High resolution MS(FAB) Calc. m/z for m⁺ 485.1984, observed m/z 485.1980.

Example 46D

N-[1-[(4'-butoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

A solution of example 46C (127 mg, 0.262 mmol) in methanol (2 mL), and PH 7 buffer (1 mL) at 0°C was treated with oxone (402 mg, 0.655 mmol) for 30 minutes then ambient temperature for 1 hour, neutralized with saturated sodium bicarbonate, extracted with dichloromethane, combined extracts were washed with brine; dried (Na₂SO₄), filtered, and concentrated. The crude mixture was purified on silica gel with 50% ethyl acetate/hexane then 10% methanol/dichloromethane to provide 82 mg (60%) of the title compound as an white solid.

¹H NMR (300 MHz, DMSO-d₆) δ ; 0.92-0.97 (t, 3H, 7.5Hz), 1.20, 1.22 (s+s, 6H), 1.42-1.52 (m, 2H), 1.68-1.77 (m, 2H), 3.41-3.72 (m, 3.5H), 4.02-4.06 (t, 2H, 6.6Hz), 4.52 (m, 0.5H), 4.89 (m, 0.5H), 7.05-7.08 (d, 2H, 8.4Hz), 7.70-7.74 (2H), 7.91 (s, 3.5H), 8.10 (s, 0.5H), 8.32-8.35 (d, 1H, 9.6Hz), 9.48 (s, 0.5H), 9.62 (s, 0.5H);

MS (ESI) m/e 518 (M+H)⁺, 535 (M+NH₄)⁺, 516 (M-H)⁻, 552 (M+Cl)⁻;

Anal. calcd for C₂₅H₂₈N₄O₆·0.25H₂O: C, 57.51; H, 6.08; N, 8.04. Found: C, 57.78; H, 6.18; N, 7.84.

Example 47

N-[1-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-3-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)propyl]-N-hydroxyformamide

Example 47A

1-bromo-4-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)butan-2-one

To a suspension of CuBr₂ (1.91g, 8.5 mmol) and lithium bromide (1.48g, 17 mmol) in THF (10 mL) was added a solution of 1.06g(5.3 mmol) of 1-((1',2'Oxiranyl)propyl)-4,4-dimethyl-2,5-dioxoimidazolidine(prepared from example 5A following the procedure of

example5C) in 15 mL of THF. The reaction mixture was stirred for 2 h at room temperature, then partitioned between ethyl acetate and pH 7 buffer. The organic extract was washed with brine, dried and concentrated. The residue was filtered through a plug of silica eluting with ethyl acetate, and the filtrate was concentrated to give a white solid, which was dissolved in acetone (25 mL), cooled to 0° C, then treated with 2.5 mL of 8M Jones reagent and stirred at room temperature for 3h. The reaction was quenched with 2 mL isopropanol, then partitioned between ethyl acetate and water. The organic extract was washed with brine, dried, filtered, and concentrated. The residue was filtered through a plug of silica eluting with ethyl acetate, and the filtrate was concentrated to give the title compound.

Example 47B

N-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-3-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)propyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 16C and 16E, except substituting 47A for 16B and 4'-hydroxy-4-biphenylcarbonitrile for 4-bromophenol in example 16C.

mp 202-204 °C;

¹H NMR (300 MHz, DMSO-d₆) δ : 1.272 (6H), 1.70-2.00 (m, 2H), 3.38-3.46 (t, 2H, J=6 Hz), 3.92-4.18 (m, 2.5H), 4.46-4.57 (m, 0.5H), 7.03-7.06 (d, 2H, J=8.7 Hz), 7.695-7.724 (d, 2H, J=8.7 Hz), 7.82-7.92 (m, 6.5H), 8.26-8.35 (1.5H), 9.75(s), 9.96 (s, 1H);

MS (ESI) m/e 437 (M+H)⁺, 454 (M+NH₄)⁺, 459 (M-H)⁻;

Anal. calcd for C₂₅H₂₈N₄O₆·0.25H₂O: C, 62.64; H, 5.60; N, 12.70. Found: C, 62.55; H, 5.47; N, 12.65

Example 48

N-[1-[[[4'-(methylsulfonyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 48A

1-(4'-(thiomethyl)[1,1'-biphenyl]-4-yl)oxy)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-propanone

A solution of 4'-hydroxy-4-biphenylmethylsulfide (1.18 g, 5.47 mmol) in DMF (25 mL) at ambient temperature was treated with cesium carbonate (2.23g, 6.84 mmol) for 20 minutes, treated in a single portion with 23A (1.2 g, 4.56 mmol), stirred for 2 hours at ambient temperature and diluted with water, extracted with ethyl acetate, the combined extracts were washed with water and brine, dried (Na₂SO₄), filtered, concentrated and

purified on silica gel with 50 to 80% ethyl acetate/hexane to provide 1.0 g (55%) of the title compound as a white solid.

MS (APCI) m/e 399 (M+H)⁺, 416 (M+NH₄)⁺, 397 (M-H)⁻, 433 (M+Cl)⁻.

Example 48B

N-[1-[[[4'-(thiomethyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared from 48A following the procedures described in example 2D, 2E, 2F.

MS (ESI) m/e 444 (M+H)⁺, 461 (M+NH₄)⁺, 466 (M+Na)⁺, 442 (M-H)⁻.

Example 48C

N-[1-[[[4'-(methylsulfonyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

A solution of example 48B (440 mg, 0.993 mmol) in methanol (100 mL) and water (50 mL) at 0°C was treated with oxone (1.27 g, 2.06 mmol) and sodium bicarbonate (174 mg, 2.06 mmol) for 1 hour then ambient temperature for 1.5 hour, diluted with water, extracted with dichloromethane, combined extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated. The crude mixture was purified on silica gel with 80% ethyl acetate/hexane then 10% methanol/dichloromethane then recrystallized from dichloromethane/hexane to provide 375 mg (79%) of the title compound as an off-white solid.

¹H NMR (300 MHz, DMSO-d₆) δ : 1.26-1.27 (s+s, 6H), 3.24 (s, 3H), 3.53-3.80 (m, 2H), 4.08-4.24 (m, 2H), 4.37-4.48 (m, 0.5H), 4.80-4.92 (m, 0.5H), 7.04-7.08 (dd, 2H, J=3, 8.4 Hz), 7.72-7.75 (d, 2H, J=8.7 Hz), 7.89-8.00 (4.5H), 8.33-8.40 (1.5H), 9.56 (s, 0.5H), 9.88 (s, 0.5H);

MS (ESI) m/e 476 (M+H)⁺, 493 (M+NH₄)⁺, 474 (M-H)⁻, 510 (M+Cl)⁻.

Example 49

N-[1-[[[3'-cyano[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-N-hydroxyformamide

Example 49A

1-(4'-Cyano-[1,1'-biphenyl]-4-yl)oxy)-3-(2,5-dioxopyrrolidin-1-yl)-2-propanone

The title compound was prepared as in Example 3C, except using potassium succinimide (0.10 g, 0.95 mmol) in place of potassium phthalimide. Purification by trituration with ethyl acetate provided 0.19 g (68%) of the title compound as a white solid. MS (APCI) m/e 383 (M+Cl)⁺.

Example 49B

(-[1-(4'-Cyano-[1,1'-biphenyl]-4-yl)oxy]-3-(2,5-dioxopyrrolidin-1-yl)-prop-2-yl)hydroxylamine

The title compound was prepared from 49A using the procedure described in Example 2D and 2E.

Example 49C

N-[1-[(3'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared from 49B using the procedure described in Example 2F. mp 128 °C;

¹H NMR (300MHz, d6-DMSO) δ 10.01 (s, 0.5H), 9.63 (s, 0.5H), 8.34 (s, 0.5H), 7.98 (s, 0.5H), 7.90-7.82 (m, 4H), 7.73 (d, 2H, J=8.8 Hz), 7.06-6.89 (m, 2H), 4.90-4.78 (m, 0.5H), 4.37-4.24 (m, 0.5H), 4.22-4.04 (m, 2H), 3.74-3.60 (m, 2H), 2.65-2.61 (m, 4H);

MS (ESI) m/e 394 (M+H)⁺, 411 (M+NH₄)⁺, 392 (M-1)⁺;

Anal. Calcd for: C₂₁H₁₉N₃O₅•H₂O: C, 61.30; H, 5.14; N, 10.21. Found: C, 61.20; H, 5.03; N, 10.03.

Example 50

N-[1-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(4,4-dimethyl-2,6-dioxo-1-piperidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared as in Example 49, except using potassium 3,3-dimethylglutarimide (0.16 g, 1.1 mmol) in place of potassium succinimide.

mp 121 °C;

¹H NMR (d6-DMSO) δ 9.88-9.78 (s, 0.5H), 9.60-9.52 (s, 0.5H), 8.31 (s, 0.5H), 7.95 (s, 0.5H), 7.90-7.82 (m, 4H), 7.73 (d, 2H, J=8.9 Hz), 7.02 (d, 2H, J=8.8 Hz), 4.88-4.77 (s, 1H), 4.30-3.78 (m, 4H), 2.56 (s, 4H), 0.98 (s, 6H);

MS (ESI) 436 (M+H)⁺, 458 (M+Na)⁺, 434 (M-H)⁺.

Examples 51 and 52

N-[1S-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-N-hydroxyformamide

N-[1R-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-N-hydroxyformamide

Example 51A and 52A

A solution of Example 49B (0.2 g, 0.55 mmol), D-Mannose diacetonide (0.13 g, 0.50 mmol), and acetic acid (0.03 mL, 0.50 mmol) in CHCl_3 (5 mL) were heated at reflux for 16h, cooled, and partitioned between CH_2Cl_2 and saturated aqueous sodium bicarbonate. The organic layer was washed sequentially with water and brine, dried (MgSO_4), filtered, and concentrated. Purification by HPLC provided the two enantiomers 51A (31%) and 52A (16%).

Example 51B

A solution of 51A in MeOH (1 mL) and HCl(conc) (0.5 mL) was stirred at ambient temperature for 15 min, treated with saturated aqueous sodium bicarbonate, and partitioned between ethyl acetate and water. The organic layer was dried (MgSO_4), filtered, and concentrated to provide 0.014 g (79%) of the corresponding hydroxyl amine, which was then formylated as in Example 2F.

Example 52B

The title compound was prepared according to Example 51B but using Example 52A in place of Example 51A.

Example 53

N-[1-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3-ethyl-3-methyl-2,5-dioxo-1-pyrrolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared as in Example 49, except using potassium-3-methyl-3-ethyl succinimide (0.22 g, 1.53 mmol) in place of potassium succinimide. ^1H NMR (d_6 -DMSO) δ 9.99-9.94 (br, 0.5H), 9.64-9.58 (br, 0.5H), 8.31 (d, 0.5H, $J=1.8$ Hz), 7.93 (d, 0.5H, $J=2.9$ Hz), 7.87 (q, 4H, $J=4.1$ Hz), 7.74 (d, 2H, $J=8.9$ Hz), 7.04 (dd, 2H, $J=8.8$, 2.6 Hz), 4.93-4.81 (m, 0.5H), 4.44-4.33 (m, 0.5H), 4.24-4.05 (m, 2H), 3.85-3.71 (m, 1H), 3.62-3.53 (m, 1H), 2.69-2.38 (m, 2H), 1.64-1.46 (m, 2H), 1.18 (d, 3H, $J=4.4$ Hz), 0.85-0.75 (m, 3H); MS (ESI) 436 ($\text{M} + \text{H}$) $^+$, 434 ($\text{M} - \text{H}$) $^+$, 458 ($\text{M} + \text{Na}$) $^+$, 453 ($\text{M} + \text{NH}_4$) $^+$; Anal. Calcd for: $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_5$: C, 66.19; H, 5.78; N, 9.64. Found: C, 66.07; H, 5.85; N, 9.37.

Example 54

N-[4-[4-[(4-chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro-2H-pyran-4-yl]-N-hydroxyformamide

Example 54A

The title compound was prepared as in Example 2D but using 5,6-dihydro-2H-pyran-2-one (4.3g, 43 mmol) in place of 1-(4-(4'-carbonitrilephenyl)phenoxy)-3-thiophenoxypropan-2-one and O-Benzyl hydroxylamine in place of hydroxylamine to provide the corresponding oxime. Purification on silica gel with 1% methanol/dichloromethane provided 8.5g (96%) of the title compound as a clear liquid. MS (ESI) 207 (M+H)⁺

Example 54B

N-[4-[4-[(4-chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro-2H-pyran-4-yl]-N-benzyloxy amine

To a solution of phenoxyphenyl-4-chloro-4'-methylsulfone (0.76 g, 2.7 mmol)(preparation desribed in *J. Med. Chem.* **29**, 427-433, 1986) at -78°C was added n-BuLi (1.1 mL, 2.7 mmol). After stirring at -78°C for 15 minures, BF₃•OEt₂ was added, followed by Example 54A. After 1h, the reaction mixture was partitioned between with water and ethyl acetate, dried (MgSO₄), filtered, and concentrated. Recrystallization with ethyl acetate provided 0.41 g (35%)of the desired compound as a white solid. MS (ESI) 488 (M+H)⁺, 510 (M+Na)⁺.

Example 54C

N-[4-[4-[(4-chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro-2H-pyran-4-yl]-N-benzyloxyformamide

A solution of 54B (0.05 g, 0.10 mmol) in CH₂Cl₂ (2 mL) was treated with formic-p-methoxyphenyl anhydride, stirred at ambient temperature for 16h, treated with H₂O, and partitioned between ethyl acetate and brine. The organice layer was dried (MgSO₄), filtered, and concentrated. Purification on silica gel with 10% ethyl acetate/dichloromethane provided 0.017 g (32%) of the desired compound as a white solid MS (ESI) 516 (M+H)⁺, 533 (M+NH₄)⁺, 538 (M+Na)⁺.

Example 54D

N-[4-[4-[(4-chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro-2H-pyran-4-yl]-N-hydroxyformamide

A solution of 54C (0.017 g, 0.033 mmol) and Pd black (0.006 g) in dioxane (2 mL) and acetic acid (2 mL) was stirred under H₂ for 20 min, treated with NaHCO₃, partitioned between ethyl acetate and water. The organic layer was dried (MgSO₄), filtered, and

concentrated. Purification on silica gel with 2% MeOH/dichloromethane provided 0.002 g (14%) of the desired compound.

¹H NMR (d₆-DMSO) δ 9.50-9.45 (br, 1H), 8.19 (s, 1H), 7.90-7.86 (m, 2H), 7.53-7.50 (m, 2H), 7.22-7.18 (m, 4H), 3.70-3.58 (m, 4H), 3.55-3.44 (m, 2H), 2.22-2.07 (m, 2H), 2.07-1.91 (m, 2H);

MS (ESI) 424 (M - H)⁺, 426 (M + H)⁺, 448 (M + Na)⁺.

Example 55

N-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-[[[(2-methoxycarbonyl)phenyl]-thio]ethyl]-N-hydroxyformamide]

The title compound was prepared following the procedure from Example 2B,C, D, E, F but using methyl thiosalicylate (600 mg, 2.39 mmol) in place of thiophenol in example 2B. Mixture of two rotamers: ¹H NMR (300 MHz, d₆-DMSO) δ 10.11 (s, 1H), 9.73 (s, 1H), 8.41 (s, 1H), 7.95 (s, 1H), 7.90-7.83 (m, 10 H), 7.75-7.71 (m, 4H), 7.59-7.55 (m, 4H), 7.31-7.26 (m, 2H), 7.09-7.05 (m, 4H), 4.75 (m, 1H), 4.2804.24 (m, 4H), 4.18 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.31-3.18 (m, 4H); MS (ESI) m/e 463 (M+1)⁺; Anal. calcd for C₂₅H₂₂N₂O₅S: C, 64.92; H, 4.79; N, 6.06. Found: C, 64.69; H, 4.63; N, 5.92.

Example 56

N-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-5-[(4-methyl-2-oxo-2H-1-benzopyran-6-yl)oxy]pentyl]-N-hydroxyformamide]

Example 56A

6-(4-methyl-2-oxo-2H-1-benzopyran-6-yl)oxy]-hex-1-ene

The title compound was prepared following the procedure from Example 5A but using 6-hydroxy-4-methylcoumarin (500 mg, 2.84 mmol) in place of 5,5-dimethylhydantoin and 5-hexen-1-ol in place of 3-buten-1-ol. Purification on silica gel with 20% ethyl acetate/hexanes provided 560 mg (76%) of the title compound. ¹H NMR (300 MHz, d₆-DMSO) δ 7.34 (dd, 1H), 7.24-7.20 (m, 2H), 6.40 (d, 1H), 5.90-5.77 (m, 1H), 5.04 (dq, 1H), 4.98 (dq, 1H), 4.06 (t, 2H), 2.43 (d, 3H), 2.10 (q, 2H), 1.75 (dt, 2H), 1.53 (dt, 2H).

Example 56B

N-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-5-[(4-methyl-2-oxo-2H-1-benzopyran-6-yl)oxy]pentyl]-N-hydroxyformamide]

The title compound was prepared following the procedures from Example 5C, 1B, 2C, 2D, 2E and 2F but using 56A (500 mg, 1.94 mmol) in place of 5B in example 56B. Purification on silica gel with 50% ethyl acetate/hexanes provided 400 mg (75%) of the title compound.

- 5 Mixture of two rotamers: ^1H NMR (300 MHz, d_6 -DMSO) δ 9.89 (s, 1H), 9.51 (s, 1H), 8.42 (s, 1H), 8.03 (s, 1H), 7.86 (m, 8H), 7.73-7.70 (m, 4H), 7.34 (d, 2H), 7.24-7.21 (m, 4H), 7.08-7.04 (m, 4H), 6.40 (s, 2H), 4.60 (s, 1H), 4.18-3.99 (m, 9H), 2.43 (s, 6H), 1.86-1.54 (m, 12H);
MS (ESI) m/e 513 ($M+1$) $^+$;
10 Anal. calcd for $\text{C}_{30}\text{H}_{28}\text{N}_2\text{O}_6$: C, 70.30; H, 5.51; N, 5.47. Found: C, 70.52; H, 5.85; N, 5.20.

Example 57

N -[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-4-[(4-methyl-2-oxo-2H-1-benzopyran-6-yl)oxy]butyl]- N -hydroxyformamide

15 The title compound was prepared following the procedure from Example 56 but using 4-penten-1-ol in place of 5-hexen-1-ol in example 56A.

Mixture of two rotamers: ^1H NMR (300 MHz, d_6 -DMSO) δ 9.94 (s, 1H), 9.55 (s, 1H), 8.44 (s, 1H), 8.06 (s, 1H), 7.86 (m, 8H), 7.73-7.70 (m, 4H), 7.35 (d, 2H), 7.26-7.22 (m, 4H), 7.08-7.05 (m, 4H), 6.40 (s, 2H), 4.65 (m, 1H), 4.17-4.04 (m, 9H), 2.44 (s, 6H), 1.77 (m, 8H);

MS (ESI) m/e 499 ($M+1$) $^+$;

20 Anal. calcd for $\text{C}_{29}\text{H}_{26}\text{N}_2\text{O}_6 \cdot 0.75\text{H}_2\text{O}$: C, 68.03; H, 5.41; N, 5.47. Found: C, 68.21; H, 5.25; N, 5.28.

Example 58

N -[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-4-[(4-methyl-2-oxo-2H-1-benzopyran-7-yl)oxy]butyl]- N -hydroxyformamide

25 The title compound was prepared following the procedure from Example 56 but using 7-hydroxy-4-methylcoumarin (500 mg, 2.8 mmol) in place of 6-hydroxy-4-methylcoumarin and 4-penten-1-ol in place of 5-hexen-1-ol in example 56A.

Mixture of two rotamers: ^1H NMR (300 MHz, d_6 -DMSO) δ 9.95 (s, 1H), 9.55 (s, 1H), 9.44 (s, 1H), 8.05 (s, 1H), 7.90-7.82 (m, 8H), 7.73-7.67 (m, 6H), 7.08-7.04 (m, 4H), 7.01-6.95 (m, 4H), 6.21 (s, 2H), 4.64 (m, 1H), 4.20-4.01 (m, 9H), 2.40 (s, 6H), 1.80-1.74 (m, 8H);

35 MS (ESI) m/e 499 ($M+1$) $^+$;

Anal. calcd for C₂₉H₂₆N₂O₆: C, 69.87; H, 5.26; N, 5.62. Found: C, 69.51; H, 5.33; N, 5.40.

Example 59

N-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-5-[(4-methyl-2-oxo-2H-1-benzopyran-7-yl)oxy]pentyl]-*N*-hydroxyformamide

The title compound was prepared following the procedure from Example 56 but using 7-hydroxy-4-methylcoumarin (500 mg, 2.8 mmol) in place of 6-hydroxy-4-methylcoumarin in example 56A.

Mixture of two rotamers: ¹H NMR (300 MHz, d₆-DMSO) δ 9.89 (s, 1H), 9.50 (s, 1H), 8.42 (s, 1H), 8.03 (s, 1H), 7.90-7.82 (m, 8H), 7.73-7.66 (m, 6H), 7.08-7.03 (m, 4H), 6.98-6.94 (m, 2H), 6.21 (s, 2H), 4.60 (m, 1H), 4.15-3.98 (m, 9H), 2.40 (s, 6H), 1.84-1.40 (m, 12H);

MS (ESI) m/e 513 (M+1)⁺;

Anal. calcd for C₃₀H₂₈N₂O₆: C, 70.30; H, 5.51; N, 5.47. Found: C, 70.35; H, 5.52; N, 5.17.

Example 60

N-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(5,5-dimethyl-2,4-dioxo-3-oxazolidinyl)ethyl]-*N*-hydroxyformamide

The title compound was prepared as in Example 49, except using 5,5-dimethylloxazolidinine-2,4-dione (300 mg, 0.8 mmol) in place of succinimide.

Mixture of two rotamers: ¹H NMR (300 MHz, d₆-DMSO) δ 10.08 (s, 1H), 9.70 (s, 1H), 8.35 (s, 1H), 7.98 (s, 1H), 7.90-7.83 (m, 8H), 7.74 (d, 4H), 7.06 (d, 4H), 4.90 (m, 1H), 4.47 (m, 1H), 4.24-4.16 (m, 4H), 3.85 (d, 1H), 3.80 (d, 1H), 3.69-3.65 (m, 1H), 3.64-3.61 (m, 1H), 1.49 (s, 6H), 1.48 (s, 6H);

MS (ESI) m/e 441 (M+18)⁺.

Example 61

N-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

Example 61A

1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)thio]-3-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)-2-propanone

A solution of 4'-thiol-4-biphenylcarbonitrile (150 mg, 0.71 mmol) in 6 mL of DMF at -5 °C was treated with potassium carbonate (89 mg, 0.645 mmol) and 1-bromo-3-(3,4,4-

trimethyl-2,5-dioxo-1-imidazolidin-1-yl)-2-propanone (179 mg, 0.645 mmol), stirred 1 h at -5 °C, quenched with saturated NH₄Cl, extracted with ethyl acetate, washed with brine, dried over Na₂SO₄, filtered, and concentrated to a solid. Purification on silica gel with 1:1 ethyl acetate/hexanes provided 200 mg (75%) of the title compound.

- 5 ¹H NMR (300 MHz, d₆-DMSO) δ 7.94-7.87 (m, 4H), 7.72 (d, 2H), 7.43 (d, 2H), 4.55 (s, 2H), 4.27 (s, 2H), 2.80 (s, 3H), 1.32 (s, 6H).

Example 61B

N-[1-[(4'-cyano[1,1'-biphenyl]-4-yl)thio]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

10

The title compound was prepared from 61A following the procedures from Example 2D, 2E and 2F.

Mixture of two rotamers: ¹H NMR (300 MHz, d₆-DMSO) δ 9.76 (s, 1H), 9.51 (s, 1H), 8.29 (s, 1H), 7.93-7.87 (m, 8H), 7.75-7.72 (m, 5H), 7.50-7.44 (m, 4H), 4.60 (m, 1H), 4.10 (m, 1H), 3.80-3.60 (m, 4H), 3.25-3.15 (m, 4H), 2.77 (s, 6H), 1.25 (s, 12H).

15

Example 61C

N-[1-[(4'-cyano[1,1'-biphenyl]-4-yl)sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

20

A solution of 61B (81 mg, 0.18 mmol) in 4:1 THF/H₂O at 0 °C was treated with OXONE (140 mg) and NaHCO₃ (33 mg), stirred at 0 °C for 30 min then 23 °C for 1 h, quenched with H₂O, extracted with ethyl acetate, washed with brine, dried over Na₂SO₄, filtered, and concentrated to a white solid. Purification on silica gel with 2% methanol/dichloromethane provided 43 mg (49%) of the title compound.

25

Mixture of two rotamers: ¹H NMR (300 MHz, d₆-DMSO) δ 9.71 (s, 1H), 9.54 (s, 1H), 8.09 (s, 1H), 8.07-7.96 (m, 16H), 7.74 (s, 1H), 4.90 (m, 1H), 4.54 (m, 1H), 3.74-3.60 (m, 4H), 3.55-3.44 (m, 4H), 2.74 (s, 3H), 2.74 (s, 3H), 1.24-1.22 (m, 12H);

MS (ESI) m/e 485 (M+1)⁺;

Anal. calcd for C₂₃H₂₄N₄O₆S: C, 57.01; H, 4.99; N, 11.56. Found: C, 56.86; H, 5.21; N, 11.28.

30

Example 62

N-[1-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

35

The title compound was prepared as in Example 49, except using 1-methylhydantoin in place of succinimide.

Mixture of two rotamers: ¹H NMR (300 MHz, d₆-DMSO) δ 9.97 (s, 1H), 9.61 (s, 1H), 8.35 (s, 1H), 7.98 (s, 1H), 7.90-7.83 (m, 8H), 7.73 (d, 4H), 7.03 (d, 2H), 7.01 (d, 2H),

4.88-4.84 (m, 1H), 4.39-4.35 (m, 1H), 4.22-4.08 (m, 4H), 3.97 (s, 2H), 3.94 (s, 2H), 3.75-3.57 (m, 4H), 2.86 (s, 3H), 2.85 (s, 3H);

MS (ESI) m/e 409 (M+1)⁺;

Anal. calcd for C₂₁H₂₀N₄O₅: C, 61.76; H, 4.94; N, 13.72. Found: C, 61.47; H, 5.00; N, 13.39.

Example 63

N-[1-[(4'-cyano[1,1'-biphenyl]-4-yl)sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedure from Example 61 but using 1-bromo-3-(4,4-dimethyl-2,5-dioxo-1-imidazolidin-1-yl)-2-propanone in place of 1-bromo-3-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidin-1-yl)-2-propanone in example 61A. Mixture of two rotamers: ¹H NMR (300 MHz, d₆-DMSO) δ 9.66 (s, 1H), 9.51 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 8.07-7.96 (s, 16H), 7.74 (s, 1H), 4.94-4.86 (m, 1H), 4.58-4.50 (m, 1H), 3.80-3.37 (m, 8H), 1.23-1.20 (m, 12H);

MS (ESI) m/e 488 (M+18)⁺;

Anal. calcd for C₂₂H₂₂N₄O₆S: C, 56.16; H, 4.71; N, 11.91. Found: C, 56.12; H, 5.00; N, 11.59.

Example 64

(-)-N-[1-[(4'-chloro-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 64A

1-[4'-chloro-1',1''-biphenyl]-4'-yl)oxy]-3-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)-propan-2-one

A solution of Example 16B (0.81 g, 2.93 mmol), 4-chloro-4'-hydroxybiphenyl (0.50 g, 2.44 mmol), and potassium carbonate (0.35 g, 2.57 mmol) in dry DMF (50 mL) was stirred at ambient temperature for 1.5 hour and partitioned between ethyl acetate and water. The aqueous layer was drawn off and extracted with ethyl acetate (1x). The combined organic extracts were diluted with an equal volume of hexanes and washed sequentially with water (3x) and brine (2x), dried (Na₂SO₄), filtered, and concentrated to provide 0.89 g of a waxy clumpy solid which was purified by purified on silica gel with 40% ethyl acetate/dichloromethane to provide 0.46 g (47%) of the title compound as a colorless solid.

mp 165-166 °C;

MS (DCI/NH₃) m/e 379 (M+NH₄)⁺.

Example 64B

(-)-N-[1-[[[4'-chloro-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The ketone from Example 64B was sequentially converted to the corresponding oximes, hydroxylamine, and the final compound as described in Examples 2D, 2E, and 2F. The title compound was purified on silica gel with 2.5% methanol/dichloromethane to provide the title compound as a colorless solid which was recrystallized from ethyl acetate/hexanes.

mp 124-125 °C;

MS (DCI/NH₃) m/e 446 (M+H)⁺ and 463 (M+NH₄)⁺;

¹H NMR (300 MHz, CDCl₃) δ 9.90 (s; 0.5H), 9.58 (s; 0.5H), 8.32 (s; 0.5H), 7.92 (s; 0.5H), 7.65 (d; 2H; J=9 Hz), 7.61 (d; 2H; J=9 Hz), 7.47 (d; 2H; J=9 Hz), 6.99 (d; 1H; J=9 Hz), 6.97 (d; 1H; J=9 Hz), 4.86 (m; 0.5H), 4.42 (m; 0.5H), 4.08-4.23 (m; 2H), 3.82-3.70 (m; 1H), 3.55-3.65 (m; 1H), 2.80 (s; 1.5H), 2.78 (s; 1.5H), 1.30 (s; 3H), 1.28 (s; 3H);

Anal. calcd for C₂₂H₂₄N₃O₅Cl: C, 59.26; H, 5.42; N, 9.42. Found: C, 59.54; H, 5.61; N, 9.13.

Example 65

(+)-N-[1-[[[3'-cyanomethyl-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,5,5-trimethyl-2,4-dioxo-1-imidazolidinyl)propyl]-N-hydroxyformamide

Example 65A

1-(3-[[[3'-cyanomethyl-[1,1'-biphenyl]-4-yl]oxy]-propan-2-on-1-yl]-3,4,4-trimethyl-2,5-dioxoimidazolidine

The title compound was prepared as in Example 5F but using 4'-hydroxy-3-biphenylcarbonitrilemethane (0.95 g, 2.80 mmol) in place of 4'-hydroxy-4-biphenylcarbonitrile. Purification on silica gel with 100% ethyl acetate provided 0.78 g of title compound.

MS (DCI/NH₃) m/e 437 (M+NH₄)⁺.

Example 65B

(+)-N-[1-[[[3'-cyanomethyl-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)propyl]-N-hydroxyformamide

Example 65A (0.78 g, 1.87 mmol) was processed sequentially according to the procedures in Example 2D, 2E, and 2F without purification of the intermediates.

Purification on silica gel with 100% ethyl acetate provided 500 mg (1.08 mmol) of the title compound.

¹H NMR (300 MHz, DMSO) δ 9.99 (s, 0.5H), 9.58 (s, 0.5H), 8.36 (s, 0.5H), 7.92 (s, 0.5H), d 7.60 (m, 4H), 7.46 (t, 1H J=8 Hz), 7.30 (d, 1H; J=8 Hz), 7.02 (d, 2H; J=8 Hz), 4.50 (m, 0.5H), 4.18 (m, 0.5H), 4.12 (s, 2H), 4.10 (m, 2H), 3.45 (m, 2H), 2.80 (s, 3H), 1.92 (m, 1H), 1.80 (m, 1H), 1.30 (s, 6H);
5 MS (DCI/NH₃) m/e 482 (M+NH₄)⁺.

Example 66

(+)-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]methyl]-2-isopropylthioethyl]-N-
10 hydroxyformamide

Example 66A

(+)-1-[[[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]-3-isopropylthio-2-propanol

A solution of isopropylthiol (0.48 g, 6.4 mmol) in THF (20mL) was treated with
15 K₂CO₃ (0.5 g, 3.6 mmol). After 30 minutes, 3-[[[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]-(1,2)
oxirane (0.8 g, 3.19 mmol) was added in a single portion. The resulting solution was
stirred at 70 oC for 3 hours, quenched by adding excess aqueous sodium bicarbonate
solution and partitioned between ethyl acetate and brine. The organic layer was dried
(Na₂SO₄), filtered, and the product was purified on silica gel with 50% ethyl
20 acetate/hexanes to provide 0.9 g (2.75 mmol, 86%) of the title compound.
MS (DCI/NH₃) m/e 345 (M+NH₄)⁺ and 362 (M+NH₄+NH₃)⁺.

Example 66B

(+)-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]methyl]-2-isopropylthioethyl]-N-
25 hydroxyformamide

Example 66A was processed according to the procedures in Example 2C,2D, 2E,
and 2F providing the title compound as a light orange foam.

¹H NMR (300 MHz, DMSO) δ 9.99 (s: 0.5H), 9.60 (s: 0.5H), 8.42 (s: 0.5H), 8.04
(s:0.5H), d 7.85 (m; 4H), 7.75 (d; 2H J=9 Hz), 7.05 (d;2H; J=9 Hz), 4.63 (m; 1H), 4.17
30 (m; 3H), 3.0 (m; 1H), 2.79 (m; 1H), 1.22 (dd; 6H; J=7.50 Hz);
MS (DCI/NH₃) m/e 388 (M+NH₄)⁺.

Example 67

(+)-N-[1-[[[(3'-cyanomethyl-[1,1'-biphenyl]-4-y)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-
35 1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 67A

(+)-1-[4-(3'-cyanoemethylphenyl)phenoxy]-3-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)-2-propanol

The title compound was prepared as in Example 4A but using 4'-hydroxy-3-biphenylcarbonitrilemethane (170 mg, 0.64 mmol) and 3,5,5-trimethylhydantoin (37 mg, 0.96 mmol) in place of 4'-hydroxy-4-biphenylcarbonitrile and 5,5-dimethylhydantoin. Purification on silica gel with 100% ethyl acetate provided 130 g of title compound. MS (DCI/NH₃) m/e 415 (M+NH₄)⁺.

Example 67B

(+)-N-[1-[[[3'-cyanomethyl]-[1,1'-biphenyl]-4-y]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 67A was processed according to the procedures in Example 2C, 2D, 2E, and 2F providing the title compound.

¹H NMR (300 MHz, DMSO) δ 9.86 (s: 0.5H), 9.58 (s: 0.5H), 8.34 (s: 0.5H), 7.92 (s: 0.5H), d 7.60 (m; 4H), 7.46 (t; 1H J=8 Hz), 7.30 (d; 1H; J=8 Hz), 7.02 (d; 2H; J=8 Hz), 4.85 (m; 0.5H), 4.42 (m; 0.5H), 4.10 (m; 2H), 4.12 (s; 2H), 3.68 (m; 1H), 3.62 (m; 1H), 2.80 (s; 3H), 1.30 (s: 6H); MS (DCI/NH₃) m/e 468 (M+NH₄)⁺.

Example 68

(+)-N-[1-[[[4'-cyano-[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3-ethyl-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 68A

4,4-dimethyl-2,5-dioxo-N-(4-methoxybenzyl)imidazolidine

A solution of 4,4-dimethyl-2,5-dioxoimidazolidine (17.0 g, 133 mmol), 4-methoxybenzyl chloride (30.0 g, 192 mmol), and potassium carbonate (27.5 g, 200 mmol) in dry DMF (600 mL) was heated at 80 °C under nitrogen for 3h. The volume was reduced under high vacuum to about 1/4 of the original volume and the resulting solution was partitioned between ethyl acetate and water. The aqueous layer was drawn off and extracted with ethyl acetate (2x). The combined organic extracts were washed sequentially with water (2x) and brine (2x), dried (Na₂SO₄), filtered and concentrated under vacuum to provide 32.97 g of a solid. Pure title compound was obtained by recrystallization from ethyl acetate and hexanes to provide 24.5 g (74%) of a colorless solid. mp 109-111 °C;

MS (DCI/NH₃) m/e 249 (M+H)⁺ and 266 (M+NH₄)⁺.

Example 68B

3-Ethyl-1-(4'-methoxybenzyl)-2,5-dioxo-4,4-dimethylimidazolidine

A solution of 4,4-dimethyl-2,5-dioxo-*N*-(4-methoxybenzyl)imidazolidine (3.5 g, 14.1 mmol) in THF (100 mL) was treated with sodium hydride (0.5 g, 21.2 mmol), stirred for 10 minute, treated with iodoethane (3.3 g, 21.2 mmol), stirred at 50 °C for 3 hours. then treated with HCl solution (10%) and partitioned between ethyl acetate and brine. The organic layer was dried, filtered and concentrated to provide 3.8g (13.8 mmol, 98%) of title compound as white solid.

MS (DCI/NH₃) m/e 294 (M+NH₄)⁺.

Example 68C

3-Ethyl-2,5-dioxo-4,4-dimethylimidazolidine

A solution of 3-Ethyl-1-(4'-methoxybenzyl)-2,5-dioxo-4,4-dimethylimidazolidine (3.86 g, 14.0 mmol) in methoxybenzene (100 mL) was treated with aluminum trichloride (5.5 g, 42 mmol), stirred at 75°C for 30 minute, then poured the reaction into HCl solution (10%) and partitioned between ethyl acetate and brine. The organic layer was dried, filtered, and concentrated. Purification by recrystallization with ethyl acetate provided 2.1 g (13.5 mmol, 96%) of title compound as white solid.

MS (DCI/NH₃) m/e 174 (M+NH₄)⁺.

Example 68D

1-[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]-3-(3-ethyl-5,5-dimethyl-2,4-dioxo-1-imidazolidinyl)-2-propanone

A solution of 3-ethyl-2,5-dioxo-4,4-dimethylimidazolidine (0.7 g, 4.5 mmol) in DMF (100 mL) was treated with potassium carbonate (0.6 g, 4.5 mmol) and 1-[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]-3-bromo-2-propynone (1.0 g, 3.0 mmol), stirred at 25°C for 20 hours, then the reaction was poured into aqueous HCl solution (10%) and partitioned between ethyl acetate and brine. The organic layer was dried, filtered, and concentrated. Purification on silica gel with 50% ethyl acetate provided 0.8 g (1.97 mmol, 66%) of title compound as white solid.

MS (DCI/NH₃) m/e 424 (M+NH₄)⁺.

Example 68E

(+)-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3-ethyl-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 68B (0.72 g, 1.77 mmol) was processed sequentially according to the procedures in Example 2D, 2E, and 2F without purification of the intermediates.

- 5 Purification on silica gel with 60% ethyl acetate/hexanes provided 158 mg (0.35 mmol) of the title compound.

^1H NMR (300 MHz, DMSO) δ 9.85 (s, 0.5H), 9.54 (s, 0.5H), 8.32 (s, 0.5H), 7.94 (s, 0.5H), d 7.86 (m, 4H), 7.72 (d, 2H $J=9$ Hz), 7.08 (d, 2H, $J=9$ Hz), 4.85 (m, 0.5H), 4.42 (m, 0.5H), 4.18 (m, 2H), 3.78 (m, 1H), 3.62 (m, 1H), 1.32 (s, 6H), 1.12 (m, 3H).

- 10 MS (DCI/ NH_3) m/e 468 ($\text{M}+\text{NH}_4$) $^+$.

Example 69

(+)-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3-benzyl-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

15

Example 69A

3-benzyl-1-(4'-methoxybenzyl)-2,5-dioxo-4,4-dimethylimidazolidine

The title compound was prepared as in Example 68B but using benzyl iodine (3.9 g, 18 mmol) in place of iodoethane. Purification on silica gel with 50% ethyl acetate provided 4.0 g of title compound.

20

MS (DCI/ NH_3) m/e 356 ($\text{M}+\text{NH}_4$) $^+$.

Example 69B

3-benzyl-2,5-dioxo-4,4-dimethylimidazolidine

25

A solution of 3-benzyl-1-(4'-methoxybenzyl)-2,5-dioxo-4,4-dimethylimidazolidine (3.9 g, 11.54 mmol) in acetonitrile (100 mL) was treated with a solution of ammonium cerium nitrate (31 g, 57.7 mmol) in 65 mL of water, stirred at 25 oC for 15 minute, then diluted the reaction with ethyl acetate and partitioned between ethyl acetate and brine. The organic layer was dried, filtered, and concentrated. Purification by recrystallization with ethyl acetate/hexane provided 1.58 g (7.25 mmol, 63%) of title compound as white solid.

30

MS (DCI/ NH_3) m/e 236 ($\text{M}+\text{NH}_4$) $^+$.

Example 69C

1-[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]-3-(3-ethyl-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-propanone

35

The title compound was prepared as in Example 68D but using 3-benzyl-2,5-dioxo-4,4-dimethylimidazolidine (0.5 g, 2.28 mmol) in place of using 3-ethyl-2,5-dioxo-

4,4-dimethylimidazolidine. Purification on silica gel with 30% ethyl acetate/chloroform provided 634 mg of title compound.
MS (DCI/NH₃) m/e 485 (M+NH₄)⁺.

Example 69D

(+)-N-[1-[(4'-cyano-[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3-ethyl-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 69C (0.62 g, 1.33 mmol) was processed sequentially according to the procedures in Example 2D, 2E, and 2F without purification of the intermediates.

Purification on silica gel with 70% ethyl acetate/hexanes provided 230 mg (0.45 mmol) of the title compound.

¹H NMR (300 MHz, DMSO) δ 9.95 (s, 0.5H), 9.64 (s, 0.5H), 8.35 (s, 0.5H), 7.94 (s, 0.5H), d 7.86 (m, 4H), 7.75 (d, 2H, J=9 Hz), 7.30 (d, 2H, J=9 Hz), 7.25 (m, 3H), 7.06 (m, 2H), 4.90 (m, 0.5H), 4.52 (s, 2H), 4.50 (m, 0.5H), 4.18 (m, 2H), 3.82 (m, 1H), 3.62 (m, 1H), 1.22 (s, 6H);

MS (DCI/NH₃) m/e 530 (M+NH₄)⁺.

Example 70

(+)-N-[1-[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]methyl]-2-(3,5,5-trimethyl-2,4-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 70A

1-[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]-3-(3,5,5-trimethyl-2,4-dioxo-1-imidazolidinyl)-2-propanol

A solution of 5,5-dimethylhydantoin (2.0 g, 15.6 mmol) in DMF (20 mL) was treated with sodium tert-butoxide (1.5 g, 15.6 mmol), stirred for 10 minute, treated with iodomethane (2.2 g, 15.6 mmol), stirred at 40 °C for 3 hours. The resulting solution was treated with sodium tert-butoxide (1.5 g, 15.6 mmol) followed by 3-[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]-(1,2) oxirane (1.15 g, 4.58 mmol), stirred at 100 °C for 20 minute, treated with HCl solution (10%) and partitioned between ethyl acetate and brine. The organic layer was dried and concentrated to provide 1.35g (75%) of title compound as white solid.

MS (DCI/NH₃) m/e 411 (M+NH₄).

Example 70B

1-[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]-3-(3,5,5-trimethyl-2,4-dioxo-1-imidazolidinyl)-2-propanone

Example 70A (1.35 g, 3.4 mmol) was processed according to the procedures in Example 2C. Purification on silica gel with 30% ethyl acetate provided 1.2 g (3.1 mmol, 90%) of the title compound.
MS (DCI/NH₃) m/e 409 (M+NH₄)⁺.

5

Example 70C

(+)-N-[1-[[[(4'-cyano-[1,1'-biphenyl]-4-y)oxy]methyl]-2-(3,5,5-trimethyl-2,4-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example A-264890.0-B (1.2 g, 3.07 mmol) was processed sequentially according to the procedures in Example 2D, 2E, and 2F without purification of the intermediates. Purification on silica gel with 30% ethyl acetate/hexanes provided 380 mg (2.29 mmol) of the title compound.

¹H NMR (300 MHz, DMSO) δ 9.90 (s, 0.5H), 9.68 (s, 0.5H), 8.38 (s, 0.5H), 7.98 (s, 0.5H), d 7.88 (m, 4H), 7.72 (d, 2H, J=9 Hz), 7.08 (d, 2H, J=9 Hz), 4.92 (m, 0.5H), 4.42 (m, 0.5H), 4.20 (m, 2H), 3.50 (m, 2H), 2.88 (s, 3H), 1.32 (s, 6H);
MS (DCI/NH₃) m/e 454 (M+NH₄)⁺.

15

Example 71

N-[1-[[[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]ethyl]-N-hydroxyformamide

20

Example 71A

4'-methoxy-4-thiomethyl biphenyl

A solution of 4-bromothioanisole (6.15 g, 29.4 mmol) in DMF (60 mL) was treated sequentially with palladium (II) acetate (0.34 g, 1.5 mmol) and tri-*o*-tolylphosphine (0.94 g, 3.0 mmol) then 4-methoxyphenylboronic acid (5.06 g, 32.3 mmol) and cesium carbonate (19.2 g, 58.8 mmol). The mixture was stirred at 75°C for 8 hours, then rt for 15 hours. The resulting suspension was partitioned between water and ether/hexane, 2:1. The organic layer was dried with Mg₂SO₄, filtered, and concentrated to provide crude product as a yellow solid. Recrystallization in ether at -20 °C afforded 2.61 g (39%) of the title compound.
MS (ESI⁺) m/e 231 (M+H).

30

Example 71B

4-(4'-methoxyphenyl)-phenyl methyl sulfone

A solution of Example 71A (2.61g, 11.3 mmol) in chloroform (100 mL) was treated with *m*-chloroperbenzoic acid (6.52 g, 22.7 mmol), stirred at 0°C for 3 hours and then warmed to 10°C over 1 hour. The mixture was partitioned between dilute sodium

35

bicarbonate aqueous solution and chloroform, dried (MgSO₄), filtered, and concentrated to provide crude product as a white solid. Recrystallized in dichloromethane and ether to afford 1.89 g (64%) of the title compound.

MS (ESI+) m/e 263 (M+H) and 280 (M+NH₄).

Example 71C

N-[1-[[[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]ethyl]-N-benzyloxy amine

A suspension of Example 71B (0.26 g, 1.0 mmol) in THF (40 mL) cooled to -78°C under argon atmosphere was treated with *n*-BuLi (0.40 mL of a 2.5 M solution in hexane, 1.0 mmol) and stirred for 3 hours. The resulting suspension was treated with BF₃•Et₂O (0.127 mL, 1.0 mmol) then the O-Benzyloxime of acetaldehyde (0.15 g, 1.0 mmol) (Stewart, et. al. *J. Med. Chem.* 1997, vol. 40, number 13, pages 1955-1968) in THF (10 mL), and stirred 1 hour at -78°C and 1 hour at 25 °C. The mixture was partitioned between ether and pH 7 phosphate buffer. The organic extracts were washed with brine, dried (Mg₂SO₄), filtered, and concentrated to afford crude product as a white powder which was purified on silica gel with dichloromethane/methanol to provide 0.15 g (36%) of the title compound.

MS (ESI+) m/e 412 (M+H).

Example 71D

N-[1-[[[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]ethyl]-N-benzyloxyformamide

A solution of Example 71c (0.11 g, 0.27 mmol) in THF (50 mL) cooled to 0°C under argon atmosphere was treated with formic acetic anhydride (0.24 g, 2.7 mmol), stirred for 5 minutes at 0 °C then rt for 16 hours. Partitioned between 1 N Hcl and ethyl acetate. Washed organic extracts with brine, dried (Mg₂SO₄), filtered, and concentrated to provide crude oil product which was purified on silica gel with dichloromethane/methanol to afford 114 mg (96%) of the title compound.

MS (ESI+) m/e 440 (M+H) and 457 (M+NH₄).

Example 71E

N-[1-[[[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]ethyl]-N-hydroxyformamide

A solution of Example 71D (114 mg, 0.26 mmol) in THF (20 mL) was treated with 10% palladium on carbon (35 mg, catalytic amount) and hydrogen gas at atmospheric pressure and stirred at rt for 18 hours. Filtered the suspension through Celite pad and concentrated to provide crude product as a white solid which was purified by trituration in ethyl acetate to afford 66 mg (73%) of the title compound.
mp 197-198°C;

1H NMR (DMSO-d6) δ 1.16 (d, 1.5H, J=6.6 Hz), 1.22 (d, 1.5H, J=6.6 Hz), 3.43-3.70 (m, 2H), 3.82 (s, 3H), 4.28-4.41 (m, 0.5H), 4.62-4.76 (m, 0.5H), 7.08 (d, 2H, J=8.7 Hz), 7.74 (d, 2H, J=8.7 Hz), 7.87-7.96 (m, 4.5H), 8.08 (s, 0.5H), 9.47 (s, 0.5H), 9.89 (s, 0.5H); MS (ESI+) m/e 350 (M+H), 367 (M+NH₄);

5 Anal. Calcd for: C₁₇H₁₉NO₃S•H₂O C, 55.57; H, 5.76; N, 3.81. Found: C, 55.32; H, 5.20; N, 3.67.

Example 72

N-[1-[[[4'-chloro[1,1'-biphenyl]-4-yl]sulfonyl]methyl]ethyl]-N-hydroxyformamide

10 The title compound was synthesized according to the procedures described in Example 71 except using 4-chlorophenylboronic acid in place of 4-methoxyphenylboronic acid in Example 71A. Purification of the crude final product by recrystallization in ethyl acetate afforded 36 mg of title compound.

mp 178-180°C;

15 1H NMR (DMSO-d6) δ 1.16 (d, 1.5H, J=6.6 Hz), 1.22 (d, 1.5H, J=6.6 Hz), 3.50 (dd, 1H, J=4.8, 14.7 Hz), 3.57-3.73 (m, 1H), 4.28-4.41 (m, 0.5H), 4.61-4.77 (m, 0.5H), 7.59 (d, 2H, J=8.4 Hz), 7.81 (d, 2H, J=8.4 Hz), 7.91 (s, 0.5H), 7.92-8.00 (m, 4H), 8.07 (s, 0.5H), 9.45 (s, 0.5H), 9.86 (s, 0.5H);

MS (ESI+) m/e 354 (M+H), 376 (M+Na);

20 Anal. Calcd for: C₁₆H₁₆NO₄SCl C, 54.31; H, 4.55; N, 3.95. Found: C, 54.46; H, 4.43; N, 3.85.

Example 73

N-[1-[[[4-(1,3-benzodioxol-5-yl)phenyl]sulfonyl]methyl]ethyl]-N-hydroxyformamide

25 The title compound was synthesized according to the procedures described in Example 71 except using 3,4-methylenedioxybenzeneboronic acid in place of 4-methoxyphenylboronic acid in Example 71A. mp 200-201°C;

1H NMR (DMSO-d6) δ 1.16 (d, 1.5H, J=6.6 Hz), 1.22 (d, 1.5H, J=6.6 Hz), 3.44-3.70 (m, 2H), 4.28-4.40 (m, 0.5H), 4.61-4.76 (m, 0.5H), 6.11 (s, 2H), 7.06 (d, 1H, J=7.8 Hz), 7.29 (d, 1H, J=8.4 Hz), 7.39 (s, 1H), 7.86-7.94 (m, 4.5H), 8.08 (s, 0.5H), 9.48 (s, 0.5H), 9.90 (s, 0.5H);

30 MS (ESI+) 364 (M+H), 381 (M+NH₄);

Anal. Calcd for: C₁₇H₁₇NO₆S C, 56.19; H, 4.71; N, 3.85. Found: C, 55.97; H, 4.62; N, 3.81.

Example 74

N-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]ethyl]-N-hydroxyformamide

Example 74A

4-chlorophenoxyphenyl methyl sulfone

A solution of 4-chlorophenol (5.54 g, 43 mmol) in DMSO (75 mL) was treated sequentially with potassium t-butoxide (5.15 g, 46 mmol) then with a solution of 4-fluorophenyl methyl sulfone (5.00 g, 29 mmol) in DMSO (25 mL), heated at 120 °C for 2 hours, cooled to rt, then partitioned between dichloromethane and 1 N sodium hydroxide, dried (Mg₂SO₄), filtered, and concentrated to give crude product as a white solid. Recrystallization from ethyl acetate and hexane afforded 5.44 g (66%) of the title compound.

MS (ESI+) m/e 300 (M+NH₄).

Example 74B

N-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]ethyl]-N-hydroxyformamide

The title compound was prepared from Example 74A according to the procedures described in Example 71C-71E. Purification of the crude final compound by recrystallization in ethyl acetate afforded 388 mg of the title compound.

mp 144-145°C;

¹H NMR (DMSO-d₆) δ 1.15 (d, 1.5H, J=6.6 Hz), 1.21 (d, 1.5H, J=6.6 Hz), 3.39-3.68 (m, 2H), 4.25-4.37 (m, 0.5H), 4.60-4.70 (m, 0.5H), 7.16-7.23 (m, 4H), 7.53 (d, 2H, J=8.9 Hz), 7.83-7.92 (m, 2.5H), 8.06 (s, 0.5H), 9.45 (s, 0.5H), 9.87 (s, 0.5H);

MS (ESI+) 370 (M+H), 387 (M+NH₄);

Anal. Calcd for: C₁₆H₁₆NO₂SCl C, 51.96; H, 4.36; N, 3.78. Found: C, 52.22; H, 4.37; N, 3.80.

Example 75

N-[1-[[[4'-(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]propyl]-N-hydroxyformamide

Example 75A

1-(4'-(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl)-2-butanol

A solution of Example 71B (0.70 g, 2.67 mmol) in THF (200 mL) cooled to -78°C under argon was treated with *n*-BuLi (1.17 mL of 2.5 M solution in hexane, 2.93 mmol), stirred 4 hours at -78°C, then treated with propionaldehyde (0.40 mL, 5.34 mmol) dropwise. Allowed reaction mixture to warm to rt over 1.5 hour, quenched with saturated aqueous NH₄Cl solution (50 mL), partitioned between ether and water, dried (Mg₂SO₄), filtered, and concentrated to afford 0.90 g of crude product which was purified on silica gel with dichloromethane/methanol to provide 0.78 g (91%) of the title compound. MS (ESI+) m/e 321 (M+H), 338 (M+NH₄).

Example 75B

1-(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]-1-butene

A solution of Example 75A (0.45 g, 1.40 mmol) in dichloromethane (40 mL) cooled to 0°C was treated sequentially with triethylamine (0.29 mL, 2.11 mmol) and methanesulfonyl chloride (0.12 mL, 1.55 mmol) dropwise. Stirred at rt for 3 hours then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.21 mL, 1.40 mmol), refluxed for 2 hours, cooled to rt, and partitioned between dilute sodium bicarbonate solution and dichloromethane. The organic extract was washed with 1 N HCl, then brine, dried (Mg₂SO₄), filtered, and concentrated to afford white solid crude product. Recrystallization in ether at -20 °C provided 0.34 g (80%) of title compound. MS (ESI+) m/e 303 (M+H), 320 (M+NH₄).

Example 75C

N-[1-[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]propyl]-N-hydroxy amine

A solution of Example 75B (0.34 g, 1.12 mmol) in THF (40 mL) was treated with hydroxylamine hydrochloride (0.39 g, 5.62 mmol) and potassium carbonate (0.78 g, 5.62 mmol), refluxed for 5 hours, cooled to rt, partitioned between ether and water, dried (Mg₂SO₄), and concentrated to give crude product as a clear, colorless oil. Recrystallization from ethyl acetate and ether provided 0.25 g (67%) of the title compound. MS (ESI+) m/e 336 (M+H).

Example 75D

N-[1-[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]methyl]propyl]-N-hydroxyformamide

A solution of Example 75C (0.24 g, 0.72 mmol) in THF (30mL) cooled to 0°C was treated with formic acetic anhydride (64 mg, 0.72 mmol), stirred for 2 hours, partitioned between water and dichloromethane, dried (Mg₂SO₄), filtered, and concentrated to afford 0.25 g of crude product which was recrystallized in ethyl acetate to provide 106 mg (41%) of the title compound. mp 199-200°C; ¹H NMR (DMSO-d₆) δ 0.69-0.80 (m, 3H), 1.40-1.69 (m, 2H), 3.41-3.69 (m, 2H), 3.82 (s, 3H), 3.96-4.07 (m, 0.5H), 4.43-4.54 (m, 0.5H), 7.08 (d, 2H, J=9.0 Hz), 7.71-7.78 (m, 2H), 7.87-7.96 (m, 4.5H), 8.17 (s, 0.5H), 9.49 (s, 0.5H), 9.84 (s, 0.5H); MS (ESI+) 364 (M+H), 381 (M+NH₄); Anal. Calcd for: C₁₈H₂₁NO₃S C, 59.48; H, 5.82; N, 3.85. Found: C, 59.67; H, 5.77; N, 3.80.

Example 76

N-[1-[1,1-dimethyl-2-[(4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)sulfonyl]ethyl]-N-hydroxyformamide

5

Example 76A

4-(4'-trifluoromethylphenyl)-phenyl methyl sulfone

The title compound was prepared according to the procedure given in Example 73A substituting 4-trifluoromethylphenylboronic acid for 3,4-methylenedioxybenzeneboronic acid. Purification by recrystallization in ethyl acetate and ether afforded 3.70 g (72%) of the title compound.
MS (ESI+) m/e 318 (M+NH₄).

10

Example 76B

1-(4'-trifluoromethyl[1,1'-biphenyl]-4-yl)sulfonyl]-2-methyl-2-propanol

The title compound was prepared according to the procedure described in Example 75A substituting Example 76A for Example 71B and substituting acetone for propionaldehyde. Purification of crude product by recrystallization in ethyl acetate, ether, and pentane provided 1.40 g (73%) of the title compound.
MS (ESI+) m/e 376 (M+NH₄).

15

20

Example 76C

N-[1-[1,1-dimethyl-2-[(4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared from Example 76B according to the procedures described in Examples 75B, 75C and 75D. Purification of the final product by recrystallization in ethyl acetate and ether provided 17 mg of the title compound.
mp 167-169°C;
1H NMR (DMSO-d₆) δ 1.52 (s, 6H), 3.71 (s, 2H), 7.83-8.03 (m, 8.5H), 8.17 (s, 0.5H), 9.43 (s, 0.5H), 10.0 (s, 0.5H);
MS (ESI+) 402 (M+H), 419 (M+NH₄), 424 (M+Na);
Anal. Calcd for: C₁₈H₁₈NO₄F₃SC, 53.86; H, 4.52; N, 3.48. Found: C, 53.58; H, 4.48; N, 3.19.

25

30

Example 77

N-[1-[(phenylmethoxy)methyl]-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)sulfonyl]ethyl]-N-hydroxyformamide

35

The title compound was synthesized according to the procedures described in Examples 75A-75D except substituting Example 76A for Example 71B and substituting benzyloxyacetaldehyde for propionaldehyde in Example 75A. Purification of the crude final product by recrystallization in ethyl acetate afforded 0.53 g of title compound.

mp 172°C;

¹H NMR (DMSO-d₆) δ 3.37-3.61 (m, 3H), 3.61-3.72 (m, 1H), 4.28-4.50 (m, 2.5H), 4.81-4.93 (m, 0.5H), 7.20-7.35 (m, 5H), 7.85-8.06 (m, 8.5H), 8.18 (s, 0.5H), 9.57 (s, 0.5H), 9.96 (s, 0.5H);

MS (ESI+) 494 (M+H), 511 (M+NH₄);

Anal. Calcd for: C₂₄H₂₂NO₃F₃S C, 58.41; H, 4.49; N, 2.83. Found: C, 58.43; H, 4.54; N, 2.77.

Example 78

N-[1-(hydroxymethyl)-2-[(4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)sulfonyl]ethyl]-N-hydroxyformamide

A solution of Example 78 (35 mg, 0.07 mmol) in THF (3 mL) and methanol (5 mL) was treated with palladium on carbon, 10% (30 mg, 0.03 mmol) and hydrogen gas at atmospheric pressure, stirred at rt for 16 hours, filtered through Celite, and concentrated to afford crude product. Purification by recrystallizations in ethyl acetate, ether, and hexane provided 20 mg (70%) of the title compound.

mp 159-161°C;

¹H NMR (DMSO-d₆) δ 3.25-3.68 (m, 4H), 3.98-4.10 (m, 0.5H), 4.54-4.66 (m, 0.5H), 4.97-5.09 (m, 1H), 7.81-8.07 (m, 8.5H), 8.14 (s, 0.5H), 9.44 (s, 0.5H), 9.85 (s, 0.5H);

MS (ESI+) 404 (M+H), 421 (M+NH₄), 426 (M+Na);

Anal. Calcd for: C₁₇H₁₆NO₃F₃S C, 50.61; H, 3.99; N, 3.47. Found: C, 50.57; H, 3.93; N, 3.37.

Example 79

N-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[(4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)thio]ethyl]-N-hydroxyformamide

Example 79A

1-[(4'-trifluoromethyl)[1,1'-biphenyl]-4-yl]thio]-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-propanone

The mixture of example 46A (698mg, 1.88 mmol), tetrakis(triphenylphosphine) palladium(0) (217 mg, 0.19 mmol), 4-triflorophenylboronic acid (714 mg, 3.76 mmol) and NaOH (1M, 3.76 mL, 3.76 mmol) in DME (20 mL) was refluxed under argon for 4 hour. The mixture was evaporated to a small volume, and partitioned between CH₂Cl₂/brine.

The CH₂Cl₂ layer was collected, dried (Na₂SO₄), filtered and evaporated to dryness. Purification of the crude final product on silica gel with 20%-40% ethyl acetate/CH₂Cl₂ provided 0.820 g of the title compound. MS (DCI/NH₃) m/e 454 (M+NH₄)⁺, 437 (M+H)⁺.

5

Example 79B

N-[1-[(4,4-dimethy-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]thio]ethyl]-N-hydroxyformamide

The title compound was obtained following the procedures in Examples 2D-F (inclusive) but substituting Example 79A (0.82 g, 1.88 mmol) for Example 2C. Purification of the crude final product on silica gel with 5% methanol/dichloromethane provided 434 mg of the title compound.

mp 172-174 °C;

¹H NMR (300 MHz, d₆-DMSO) δ 9.75 and 9.52 (br s, 1H), 8.37 and 8.33 (s, 1H), 8.31 and 7.77 (s, 1H), 7.90 (d, 2H, J = 8.4 Hz), 7.81 (d, 2H, J = 8.4 Hz), 7.71 (m, 2H), 7.47 (m 2H), 4.60 and 4.09 (m, 1H), 3.52-3.77 (m, 2H), 3.08-3.46 (m, 2H), 1.28 and 1.25 and 1.23 (s, 6H);

MS (DCI/NH₃) m/e 499 (M+NH₄)⁺, 482 (M+H)⁺;

Anal. calcd for C₂₂H₂₂F₃N₃O₄S • 0.5 CH₃OH: C, 54.31; H, 4.86; N, 8.44. Found: C, 54.43; H, 4.82; N, 8.08.

10

15

20

Example 80

N-[1-[(4,4-dimethy-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]-N-hydroxyformamide

Example 79 was converted to example 80 following the procedure described in example 46D.

mp 180-182 °C;

¹H NMR (300 MHz, d₆-DMSO) δ 9.66 and 9.51 (br s, 1H), 8.39 and 8.35 (s, 1H), 8.10 and 7.73 (s, 1H), 7.79-8.02 (m, 6H), 7.89 (d, 2H, J = 8.4 Hz), 4.91 and 4.55 (m, 1H), 3.45-3.80 (m, 4H), 1.24 and 1.23 and 1.21 (s, 6H).

MS (DCI/NH₃) m/e 531 (M+NH₄)⁺, 514 (M+H)⁺;

Anal. calcd for C₂₂H₂₂F₃N₃O₆S • 0.75 H₂O: C, 50.14; H, 4.49; N, 7.97. Found: C, 50.27; H, 4.49; N, 7.97.

25

30

35

Example 81

N-[1-[(2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-N-hydroxyformamide

Example 81A

1-bromo-3-(2,5-dioxoimidazolidin-1-yl)propan-2-one

The title compound was prepared following the procedures in examples 16A and 16B, but substituting hydantoin for 1,5,5-trimethylhydantoin.

Example 81B

N-[1-[(2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-N-hydroxyformamide

The title compound was prepared following the sequence described in described in examples 16C and 16E, but substituting 81A for 16B and 4-(4'-trifluoromethoxy-phenyl)-phenol for 4-bromophenol.

¹H NMR (DMSO- δ_6) δ 9.92 (s, 0.5H), 9.60 (bs, 0.5H), 8.31 (s, 0.5H), 8.16 (s, 0.5H), 8.14 (s, 0.5H), 7.92 (s, 0.5H), 7.76-7.72 (m, 4H), 7.64-7.62 (d, 4H, J=8.4 Hz), 7.42-7.40 (d, 4H, J=8.6 Hz), 7.02-6.98 (m, 4H), 4.84-4.82 (m, 0.5H), 4.38-4.35 (m, 0.5H), 4.19-4.04 (4H); Anal. Calcd for: C₂₀H₁₈N₃O₆F₃: C, 52.98; H, 4.00; N, 9.13. Found: C, 53.01; H, 4.03; N, 9.13.

Example 82

N-[1-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures described in example 46A, 46B, 46C and 46D, except substituting example 16B for 23A in example 46A and 4-trifluoromethylbenzeneboronic acid for 4-butyloxybenzeneboronic acid in example 46B.

¹H NMR (d₆-DMSO) δ 9.70 (s, 0.5H), 9.54 (s, 0.5H), 8.10 (s, 0.5H), 8.05-7.97 (m, 6H), 7.89 (d, 2H, J=7.8 Hz), 7.75 (s, 0.5H), 4.97-4.86 (m, 0.5H), 4.60-4.48 (m, 0.5H), 3.80-3.44 (m, 4H), 2.75 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H); MS (ESI) 528 (M+H), 545 (M+NH₄), 526 (M-H); Anal. Calcd for: C₂₃H₂₄N₃O₆SF₃ C, 52.36; H, 4.58; N, 7.96. Found: C, 52.05; H, 4.70; N, 7.63.

Example 83

N-[1-[[4'-(4'-butyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures described in example 16C and 16E, except substituting example 26A for 16B and 4-(4'-butylphenyl)phenol for 4-bromophenol.

¹H NMR (d6-DMSO) δ 10.00-9.94 (br, 0.5H), 9.64-9.58 (br, 0.5H), 8.34 (s, 0.5H), 7.98 (s, 0.5H), 7.58 (d, 2H, J=8.8 Hz), 7.52 (d, 2H, J=8.6 Hz), 7.24 (d, 2H, J=8.5 Hz), 7.00-6.92 (m, 2H), 4.92-4.79 (m, 0.5H), 4.41-4.30 (m, 0.5H), 4.20-4.03 (m, 2H), 3.95 (d, 2H, J=7.8 Hz), 3.75-3.57 (m, 2H), 2.86 (s, 1.5H), 2.85 (s, 1.5H), 2.60 (t, 2H, J=7.4 Hz), 1.63-1.51 (m, 2H), 1.39-1.25 (m, 2H), 0.91 (t, 3H, J=7.4 Hz);
 MS (ESI) 440 (M+H), 457 (M+NH₄), 438 (M-H);
 Anal. Calcd for: C₂₄H₂₉N₃O₅•0.25 H₂O C, 64.92; H, 6.69; N, 9.46. Found: C, 64.76; H, 6.62; N, 9.29.

Example 84

N-[1-[(3-methoxy-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethoxy)]-1,1'-biphenyl]-4-yl]oxyethyl]-N-hydroxyformamide

The title compound was prepared following the procedures described in example 16C and 16E, except substituting example 26A for 16B and 4-(4'-trifluoromethoxy)phenol for 4-bromophenol.

¹H NMR (d6-DMSO) δ 10.02-9.92 (br, 0.5H), 9.64-9.58 (br, 0.5H), 8.35 (s, 0.5H), 7.98 (s, 0.5H), 7.74 (d, 2H, J=8.9 Hz), 7.64 (d, 2H, J=8.8 Hz), 7.41 (d, 2H, J=8.1 Hz), 7.03-6.97 (m, 2H), 4.91-4.82 (m, 0.5H), 4.41-4.31 (m, 0.5H), 4.21-4.07 (m, 2H), 3.96 (d, 2H, J=7.7 Hz), 3.72-3.57 (m, 2H), 2.86 (s, 1.5H), 2.85 (s, 1.5H);
 MS (ESI) 468 (M+H), 485 (M+NH₄), 466 (M-H);
 Anal. Calcd for: C₂₁H₂₀N₃O₆F₃ C, 53.96; H, 4.31; N, 8.99. Found: C, 53.85; H, 4.40; N, 8.85.

Example 85

N-[4-[4-[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]methyl]tetrahydro-2H-pyran-4-yl]-N-hydroxyformamide

Example 85A

N-[4-[4-[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]methyl]tetrahydro-2H-pyran-4-yl]-N-benzyloxy amine

The title compound was prepared following the procedure described in example 54A, except using 4'-chloro-40methylsulfone-biphenyl in place of phenoxyphenyl-4-chloro-4'-methylsulfone.

Example 85B

N-[4-[4-[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]methyl]tetrahydro-2H-pyran-4-yl]-N-hydroxy amine

A solution of 85A (0.436g, 0.92 mmol) was treated with (CF₃CO₂)₃B (4.6 mL, 1M solution in THF, 4.6 mmol), then stirred overnight at room temperature. The solution was concentrated, partitioned between ethyl acetate and aq. Na₂CO₃ and the organic layer was dried (Mg₂SO₄), filtered, concentrated and purified via column chromatography to give the title compound in 51% yield.

Example 85C

N-[4-[4-(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]methyl]tetrahydro-2H-pyran-4-yl]-N-hydroxyformamide

Example 85B was converted to the title compound using the formylation procedure of example 2F.

¹H NMR (d6-DMSO) δ 9.52-9.48 (br, 1H), 8.23 (s, 1H), 7.97 (s, 4H), 7.81 (d, 2H, J=8.4 Hz), 7.59 (d, 2H, J=8.5 Hz), 3.72 (s, 2H), 3.69-3.46 (m, 4H), 2.35-1.94 (m, 4H); MS (ESI) 410 (M+H), 427 (M+NH₄), 432 (M+Na), 408 (M-H).

Example 86

N-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures described in examples 46A, 46C and 46D, except using 4-(4'-chlorophenoxy)thiophenol instead of 4-bromothiophenol.

¹H NMR (d6-DMSO) δ 9.67 (s, 0.5H), 9.50 (s, 0.5H), 8.36 (d, 1H, J=13.2 Hz), 8.10 (s, 0.5H), 7.90 (dd, 2H, J=8.8, 3.0 Hz), 7.68 (s, 0.5H), 7.53 (d, 2H, J=8.8 Hz), 7.20 (d, 4H, J=8.8 Hz), 4.89-4.77 (m, 0.5H), 4.52-4.40 (m, 0.5H), 3.68-3.38 (m, 4H), 1.25-1.21 (m, 6H);

MS (ESI) 496 (M+H), 513 (M+NH₄), 494 (M-H);

Anal. Calcd for: C₂₁H₂₂N₃O₇SCl C, 50.85; H, 4.47; N, 8.47. Found: C, 50.53; H, 4.58; N, 8.25.

Example 87

N-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures described in examples 46A, 46C and 46D, except using 16B in place of 23A and 4-(4'-chlorophenoxy)thiophenol instead of 4-bromothiophenol.

¹H NMR (d6-DMSO) δ 9.78-9.71 (m, 0.5H), 9.58-9.49 (m, 0.5H), 8.09 (s, 0.5H), 7.89 (dd, 2H, J=5.8, 2.9 Hz), 7.68 (s, 0.5H), 7.53 (d, 2H, J=9.2 Hz), 7.20 (d, 4H, J=8.8 Hz),

4.88-4.78 (m, 0.5H), 4.50-4.38 (m, 0.5H), 3.72-3.40 (m, 4H), 2.76 (s, 1.5H), 2.76 (s, 1.5H), 1.26-1.22 (m, 6H);
MS (ESI) 510 (M+H), 527 (M+NH₄), 508 (M-H);
Anal. Calcd for: C₂₂H₂₄N₃O₇SCl C, 51.81; H, 4.74; N, 8.23. Found: C, 51.61; H, 4.90; N, 7.96.

Example 88

N-[1-[[[4-butyl][1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures described in example 46A, 46B, 46C and 46D, except substituting example 16B for 23A in example 46A and 4-nbutylbenzeneboronic acid for 4-butyloxybenzeneboronic acid in example 46B.
¹H NMR (d₆-DMSO) δ 9.70 (s, 0.5H), 9.54 (s, 0.5H), 8.10 (s, 0.5H), 7.94 (d, 4H, J=1.0 Hz), 7.73 (s, 0.5H), 7.69 (dd, 2H, J=8.1, 2.0 Hz), 7.35 (d, 2H, J=8.4 Hz), 4.96-4.86 (m, 0.5H), 4.60-4.48 (m, 0.5H), 3.77-3.42 (m, 4H), 2.75 (s, 3H), 2.64 (t, 2H, J=7.4 Hz), 1.64-1.54 (m, 2H), 1.40-1.27 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H), 0.91 (t, 3H, J=7.5 Hz);
MS (ESI) 516 (M+H), 533 (M+NH₄), 538 (M+Cl), 514 (M-H);
Anal. Calcd for: C₂₆H₃₃N₃O₆S C, 60.56; H, 6.45; N, 8.14. Found: C, 60.32; H, 6.44; N, 8.09.

Example 89

N-[1-[[[4'-butyl][1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethy-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 23B, except substituting 4-(4'-butylphenyl)-phenol in place of 4-(4'-ethoxyphenyl)-phenol.
¹H NMR (DMSO-*d*₆) δ 0.93 (t, 3H, J=8 Hz), 1.28 (s, 6H), 1.30-1.39 (m, 2H), 1.50-1.65 (m, 2H), 2.60 (t, 2H, J=7 Hz), 3.51-3.64 (m, 1H), 3.67-3.80 (m, 1H), 4.03-4.24 (m, 2H), 4.35-4.48 (m, 0.5H), 4.78-4.92 (m, 0.5H), 6.99 (dd, 2H, J=3.9 Hz), 7.25 (d, 2H, J=9 Hz), 7.53 (d, 2H, J=9 Hz), 7.58 (d, 2H, J=9 Hz), 7.94 (s, 0.5H), 8.34 (d, 1H, J=6 Hz), 8.39 (s, 0.5H), 9.55 (s, 0.5H), 9.87 (s, 0.5H);
MS (ESI-) 452 (M-H);
Anal. Calcd for: C₂₅H₃₁N₃O₅ C, 66.20; H, 6.88; N, 9.26. Found: C, 65.99; H, 6.71; N, 9.19.

Example 90

N-[1-[[[3'-(cyanomethyl)][1,1'-biphenyl]-4-yl]oxy]methyl]-2-(4,4-dimethy-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 23B, except substituting 4-(3'-cyanomethylphenyl)-phenol in place of 4-(4'-ethoxyphenyl)-phenol.

¹H NMR (DMSO-*d*₆) δ 2.80 (s, 6H), 3.52-3.83 (m, 2H), 4.10 (s, 2H), 4.12-4.25 (m, 2H), 4.38 (4.46, mH, J=0.5 Hz), 4.80-4.90 (m, 0.5H), 7.03 (dd, 2H, J=3,9 Hz), 7.30 (d, 1H, J=10 Hz), 7.48 (t, 1H, J=10 Hz), 7.57-7.66 (m, 4H), 7.93 (s, 0.5H), 8.34 (d, 1H, J=6 Hz), 8.39 (s, 0.5H), 9.55 (s, 0.5H), 9.88 (s, 0.5H);

MS (ESI-) 435 (M-H);

Anal. Calcd for: C₂₃H₂₄N₄O₅•0.25CH₃CO₂C₂H₅ C, 62.87; H, 5.71; N, 12.21. Found: C, 62.85; H, 5.80; N, 12.16.

Example 91

N-[1-[4-(2-thienyl)phenoxy]methyl]-2-[1-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

The title compound was prepared following the procedures of examples 16C and 16E, except substituting 4-(4'-(2-thienyl)phenyl)phenol for 4-bromophenol in example 16C.

¹H NMR (DMSO-*d*₆) δ 1.29 (s, 6H), 2.80 (s, 3H), 3.54-3.66 (m, 1H), 3.69-3.84 (m, 1H), 4.04-4.22 (m, 2H), 4.33-4.47 (m, 0.5H), 4.77-4.90 (m, 0.5H), 6.96 (dd, 2H, J=3,9 Hz), 7.08-7.13 (m, 1H), 7.38 (d, 1H, J=3 Hz), 7.46 (d, 1H, J=4 Hz), 7.59 (d, 2H, J=9 Hz), 7.92 (s, 0.5H), 8.31 (s, 0.5H), 9.54 (s, 0.5H), 9.86 (s, 0.5H). MS (ESI-) 416 (M-H);

Anal. Calcd for: C₂₀H₂₃N₃O₅S•0.25H₂O C, 56.92; H, 5.61; N, 9.95. Found: C, 56.65; H, 5.48; N, 9.77.

Example 92

N-[1-[(3-nitro[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

The title compound was prepared following the procedures of examples 16C and 16E, except substituting 4-phenyl-2-nitrophenol for 4-bromophenol in example 16C.

¹H NMR (DMSO-*d*₆) δ 1.28 (s, 6H), 2.80 (s, 3H), 3.54-3.65 (m, 1H), 3.70-3.88 (m, 1H), 4.22-4.39 (m, 2H), 4.40-4.50 (m, 0.5H), 4.80-4.91 (m, 0.5H), 7.34-7.41 (m, 2H), 7.43-7.52 (m, 2H), 7.71 (d, 2H, J=8 Hz), 7.87 (s, 0.5H), 8.0 (d, 1H, J=9 Hz), 8.16 (dd, 1H, J=3,6 Hz), 8.29 (s, 0.5H), 9.55 (s, 0.5H), 9.80 (s, 0.5H);

MS (ESI-) 455 (M-H);

Anal. Calcd for: C₂₂H₂₄N₄O₇ C, 57.88; H, 5.29; N, 12.27. Found: C, 57.62; H, 5.44; N, 11.95.

Example 93

N-[1-[[[(4'-methyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-[[3-(methylsulfonyl)amino]phenyl]ethyl]-N-hydroxyformamide

Example 93A

3-(methylsulfonyl)amino-1-bromo-benzene

The m-bromo aniline was dissolved in 40 mL of pyridine and cooled to 0 C followed by addition of methansulfonyl chloride dropwise via syringe. After 10 min, the solution was warmed to room temperature and stirred for 4h. Upon concentration *in vacuo* the residue was partitioned between 350 mL of H₂O and 500 mL of CH₂Cl₂ in a separatory funnel. The organics were separated and washed with 100 mL of 3N HCl, 200 mL of sat'd NaHCO₃ and dried over MgSO₄. Upon filtration and concentration in vacuo an off-white solid was obtained. This product was recrystallized from CH₂Cl₂/Hexanes to afford 6.7g (90%) of 93A as white needles.

Example 93B

3-(methylsulfonyl)amino-1-(prop-2-enyl)-benzene

Using a glass sealed vessel the sulphonamide 93A (3.0g, 12.1mmol) was suspended in 10 mL of toluene followed by addition of the allyltributyl tin reagent and bubbled with argon for 5 min. To the above suspension was added 280 mg (2 mol %) of Pd(PPh₃)₄ and the vessel sealed and heated at 120 C for 17h. After 15 min a homogeneous solution was obtained which turned dark brown after 30 min. After cooling, the catalyst was filtered off washing with CH₂Cl₂/MeOH. Concentration of the filtrate followed by purification on silica gel eluting with 10% Ethyl Acetate/Hexanes then 20% Ethyl Acetate/Hexanes afforded 93B, 0.99g (38%) as a colorless oil which solidified upon standing.

Example 93C

N-[1-[[[(4'-methyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-[[3-(methylsulfonyl)amino]phenyl]ethyl]-N-hydroxyformamide

The title compound was prepared from example 93B, first by epoxidizing as described in example 5C, then opening the epoxide with 4'-hydroxy-4-biphenylcarbonitrile as in example 5F, then following the sequence of reactions described in examples 2C through 2F.

¹H NMR (DMSO-*d*₆) δ 2.32 (s, 3H), 2.88 (d, 2H, J=6 Hz), 2.96 (s, 1H), 2.98 (s, 3H), 4.03-4.11 (m, 1H), 4.15-4.27 (m, 1,5H), 4.72-4.82 (bs, 0.5H), 6.97-7.10 (m, 4H), 7.05 (s, 1H), 7.20-7.30 (m, 3H), 7.50 (d, 2H, J=9 Hz), 7.57 (d, 2H, J=9 Hz), 7.73 (s, 0.5H), 8.25 (s, 0.5H), 9.18 (s, 0.5H), 10.01 (s, 0.5H);
MS (ESI-) 453 (M-H);

Anal. Calcd for: C₂₄H₂₆N₂O₅S C, 63.41; H, 5.76; N, 6.16. Found: C, 63.16; H, 6.12; N, 5.76.

Example 94

N-[1-[[[3-(diethylamino)carbonyl]phenyl]methyl]-2-[(4'-methyl[1,1'-biphenyl]-4-yl)oxy]ethyl]-N-hydroxyformamide

Example 94A

3-bromo-1-(N,N-diethylcarboxamide)-benzene

Diethylamine (10.0ml, 97mmol) was dissolved in 60ml of dry ethyl ether and cooled to 0° C. Benzoyl chloride (3.67ml, 28mmol) was dissolved in 10 mL of dry ethyl ether and was slowly added dropwise via syringe to the above solution. A white slurry developed upon addition and stirring was continued for 10 min at 0° C then warmed to room temperature for 1h. The mixture was poured into a separatory funnel containing 500 mL of ethyl ether and 75 mL of 10% NaOH. The organics were separated and washed a second time with 75 mL of 10% NaOH followed by 75 mL of 10% HCl then 200 mL of water. A final wash with 100 mL of brine followed by drying over MgSO₄, filtering and then concentration *in vacuo*, afforded the 94A as a colorless liquid, 5.9 g (83%) which was used without further purification.

Example 94B

N-[1-[[[3-(diethylamino)carbonyl]phenyl]methyl]-2-[(4'-methyl[1,1'-biphenyl]-4-yl)oxy]ethyl]-N-hydroxyformamide

The title compound was prepared following the procedure described in examples 93B and 93C, except substituting 94A for 93A.

¹H NMR (DMSO-*d*₆) δ 0.98-1.20 (bd, 6H), 2.32 (s, 3H), 2.93 (d, 2H, J=6 Hz), 3.11-3.48 (bd, 4H), 4.0-4.13 (m, 1H), 4.16-4.30 (m, 1.5H), 4.74-4.86 (bs, 0.5H), 6.98 (d, 2H, J=9 Hz), 7.13-7.40 (m, 6H), 7.50 (d, 2H, J=8 Hz), 7.56 (d, 2H, J=9 Hz), 7.73 (s, 0.5H), 8.23 (s, 0.5H), 9.63 (s, 0.5H), 10.02 (s, 0.5H). MS (ESI+) 461 (M+H). Anal. Calcd for: C₂₈H₃₂N₂O₄•1.5H₂O C, 68.97; H, 7.23; N, 5.74. Found: C, 68.96; H, 7.09; N, 5.42.

Example 95

N-[1-[[[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-[(4'-cyano [1,1'-biphenyl]-4-yl)oxy]ethyl]-N-hydroxyformamide

The title compound was prepared using the procedures of examples 5F,5G and 5H, except using example 3B in place of 5E.

1H NMR (DMSO- δ) δ 4.18-4.36 (m, 4H), 4.43-4.57 (bs, 0.5H), 4.97-5.03 (bs, 0.5H), 7.10 (d, 4H, J=9 Hz), 7.77 (d, 4H, J=9 Hz), 7.81-7.95 (m, 8H), 8.13 (s, 0.5H), 8.42 (s, 0.5H), 9.75 (s, 0.5H), 10.15 (s, 0.5H);
MS (DCI/NH₃) M+H (490), M+18 (507);
5 Anal. Calcd for: C₃₀H₂₃N₃O₄•0.25H₂O C, 72.93; H, 4.79; N, 8.50. Found: C, 72.80; H, 4.74; N, 8.26.

Example 96

N-[1-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

10 The title compound was prepared according to the procedures of example 23B, except substituting 4-(4'-cyanophenyl)-phenol in place of 4-(4'-ethoxyphenyl)-phenol.
1H NMR (DMSO- δ) δ 1.27 (s, 6H), 3.50-3.66 (m, 1H), 3.67-3.82 (m, 1H), 4.08-4.28 (m, 2H), 4.38-4.50 (m, 0.5H), 4.80-4.93 (m, 0.5H), 7.06 (dd, 2H, J=3,9 Hz), 7.73 (d, 2H, J=9 Hz), 7.82-7.93 (m, 4H), 7.94 (s, 0.5H), 8.35 (d, 1H, J=6 Hz), 8.40 (s, 0.5H), 9.56 (s, 0.5H),
15 9.87 (s, 0.5H);
MS (ESI-) 421 (M-H);
Anal. Calcd for: C₂₂H₂₂N₄O₅•0.25H₂O C, 61.89; H, 5.31; N, 13.12. Found: C, 61.82; H, 5.34; N, 12.82.

Example 97

20 N-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(2-methoxyethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 23B, except substituting 4-(4'-(2-methoxyethoxy)-phenyl)-phenol in place of 4-(4'-ethoxyphenyl)-phenol.
25 1H NMR (DMSO- δ) δ 1.26 (s, 6H), 3.33 (s, 3H), 3.50-3.64 (m, 1H), 3.66-3.69 (m, 2H), 3.70-3.81 (m, 1H), 4.03-4.22 (m, 4H), 4.35-4.48 (m, 0.5H), 4.78-4.90 (m, 0.5H), 6.98 (dd, 4H, J=3,9 Hz), 7.55 (dd, 4H, J=3,6 Hz), 7.91 (s, 0.5H), 8.33 (d, 1H, J=7 Hz), 8.40 (s, 0.5H), 9.55 (s, 0.5H), 9.86 (s, 0.5H);
MS (ESI-) 470 (M-1);
30 Anal. Calcd for: C₂₄H₂₉N₃O₇ C, 61.13; H, 6.19; N, 8.91. Found: C, 60.86; H, 6.41; N, 8.65.

Example 98

35 N-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[(4'-propoxy[1,1'-biphenyl]-4-yl)oxy]ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 23B, except substituting 4-(4'-propoxyphenyl)-phenol in place of 4-(4'-ethoxyphenyl)-phenol.

mp. 158-160 °C

Mass Spec. (ESI): +456 (m+H), +473 (m+18), -454 (m-H), -490 (m+35)

¹H NMR (DMSO-d₆): δ 0.90 (3H, t, J=6 Hz), 1.17 (2.4H, s), 1.20 (3.6H, s), 1.65 (2H, sextuplet, J=6 Hz), 3.46-3.55 (1H, m), 3.59-3.74 (1H, m), 3.86 (2H, t, J=6 Hz), 3.96-4.06 (1H, m), 4.06-4.14 (1H, m), 4.28-4.38 (0.6H, m), 4.72-4.81 (0.4H, m), 6.88 (4H, d, J=4.8 Hz), 7.42, (2H, d, J=4.8 Hz), 7.44 (2H, d, J=4.8 Hz), 7.83 (0.4H, s), 8.24 (1H, s), 8.28 (0.6H, s), 9.43 (0.6H, s), 9.74 (0.4H, s);

¹³C NMR (DMSO-d₆): δ 10.4, 22.0, 24.4, 24.5, 36.0, 36.4, 52.1, 56.1, 57.8, 57.9, 64.7, 65.0, 69.0, 114.8, 115.0, 127.2, 132.0, 132.8, 132.9, 155.0, 155.2, 157.0, 157.1, 157.9, 158.2, 163.1, 177.2, 177.3;

Calc. for C₂₄H₂₉N₃O₆: C, 63.28; H, 6.42; N, 9.22. Found: C, 63.25; H, 6.48; N, 9.29.

Example 99

N-[1-[(4,4-dimethy-2,5-dioxo-1-imidazolidinyl)methyl]-2-[(4'-pentyloxy[1,1'-biphenyl]-4-yl)oxy]ethyl]-*N*-hydroxyformamide

The title compound was prepared according to the procedures of example 23B, except substituting 4-(4'-pentyloxyphenyl)-phenol in place of 4-(4'-ethoxyphenyl)-phenol.

¹H NMR (300 MHz, DMSO- δ_6) δ 0.90 (t, 3H, J=6.9 Hz), 1.27 (s, 6H), 1.3-1.5 (m, 4H), 1.7-1.8 (m, 2H), 3.5-3.8 (m, 2H), 3.98 (t, 2H, J=6.9 Hz), 4.0-4.2 (m, 2H), 4.35-4.45 (m, 0.5H), 4.8-4.9 (m, 0.5H), 6.9-7.0 (m, 4H), 7.5-7.6 (m, 4H), 7.92 (s, 0.5H), 8.3-8.4 (m, 1.5H), 9.53 (s, 0.5H), 9.84 (s, 0.5H);
MS (ESI) 484 (M+H), 501 (M+NH₄);

Anal. calcd for C₂₆H₃₃N₃O₆: C, 64.57; H, 6.87; N, 8.68. Found: C, 64.27; H, 6.85; N, 8.60.

Example 100

N-[1-[[3'-(cyanomethyl)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-3-(4,4-dimethy-2,5-dioxo-1-imidazolidinyl)propyl]-*N*-hydroxyformamide

The title compound was made according to the procedures of example 61, but using example 23A in place of example 16B and 4'-thiol-3-cyanomethyl biphenyl in place of 4'-thiol-4-biphenylcarbonitrile in example 61A.

¹H NMR (300 MHz, d₆-DMSO) δ 9.98 (br, 0.5H), 9.63 (br, 0.5H), 8.31 (s, 0.5H), 8.23 (s, 0.5H), 8.12 (s, 0.5H), 7.99-7.92 (m, 4H), 7.82 (s, 0.5H), 7.74 (m, 2H), 7.57 (t, 1H), 7.46 (d, 1H), 4.52 (m, 0.5H), 4.14 (s, 2H), 4.00 (m, 0.5H), 3.69-3.57 (m, 2H), 3.42-3.28 (m, 2H), 2.02-1.88 (m, 1H), 1.78-1.64 (m, 1H), 1.21 (s, 6H);

MS (ESI) m/e 499 (M+H)⁺;

Anal. calcd for C₂₄H₂₆N₄O₆S: C, 57.82; H, 5.26; N, 11.24. Found: C, 57.56; H, 5.41; N, 10.89.

Example 101

N-[1-[[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures of example 46, except substituting example 16B for 23A in example 46A and 4-trifluoromethoxybenzeneboronic acid for 4-butoxybenzeneboronic acid in example 46B.

¹H NMR (300 MHz, d₆-DMSO) δ 9.72 (br, 0.5H), 9.56 (br, 0.5H), 8.10 (s, 0.5H), 7.99 (m, 4H), 7.94-7.88 (m, 2H), 7.74 (s, 0.5H), 7.53 (d, 2H), 4.91 (m, 0.5H), 4.54 (m, 0.5H), 3.75-3.44 (m, 4H), 2.75 (s, 3H), 1.24-1.22 (m, 6H);

MS (ESI) m/e 544 (M+H)⁺;

Anal. calcd for C₂₃H₂₄F₃N₃O₇S: C, 50.83; H, 4.45; N, 7.73. Found: C, 51.17; H, 4.77; N, 7.29.

Example 102

N-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was made according to the procedures of example 61, but using example 26A in place of example 16B in example 61A.

¹H NMR (300 MHz, d₆-DMSO) δ 9.83 (s, 0.5H), 9.58 (s, 0.5H), 8.09 (s, 0.5H), 8.04-8.00 (m, 8H), 7.80 (s, 0.5H), 4.94-4.85 (m, 0.5H), 4.52-4.43 (m, 0.5H), 3.91-3.88 (m, 2H), 3.78-3.44 (m, 4H), 2.80 (s, 1.5H), 2.79 (s, 1.5H);

MS (ESI) m/e 457 (M+H)⁺;

Anal. calcd for C₂₁H₂₀N₄O₆S: C, 55.26; H, 4.42; N, 12.27. Found: C, 54.99; H, 4.38; N, 12.07.

Example 103

N-[1-[[[3'-(cyanomethyl)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures of example 46, except substituting example 16B for 23A in example 46A and 3-cyanomethylbenzeneboronic acid for 4-butoxybenzeneboronic acid in example 46B.

The title compound was made in the usual way from the α-bromo ketone and 4-bromothiophenol.

¹H NMR (300 MHz, d₆-DMSO) δ 9.71 (s, 0.5H), 9.56 (s, 0.5H), 8.10 (s, 0.5H), 8.03-7.94 (m, 4H), 7.75 (m, 2.5H), 7.57 (t, 2H), 7.46 (d, 2H), 4.96-4.88 (m, 0.5H), 4.59-4.49 (m, 0.5H), 4.14 (s, 2H), 3.69-3.48 (m, 4H), 2.75 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H);
MS (ESI) m/e 499 (M+H)⁺;

- 5 Anal. calcd for C₂₄H₂₆N₄O₆S: C, 57.82; H, 5.26; N, 11.24. Found: C, 57.73; H, 5.36; N, 10.95.

Example 104

N-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]oxyl]methyl]-2-(1,6-dihydro-3-methyl-6-oxo-1-pyridazinyl)ethyl]-N-hydroxyformamide

10

The title compound was prepared following the procedures of example 3C and 3D, except substituting the potassium salt 6-methyl-3(2H)-pyridazinone (generated in situ with potassium carbonate) for potassium phthalimide in example 3C.

- 15 ¹H NMR (300 MHz, CD₃OD) δ 8.31 (s, 0.5H), 7.91 (s, 0.5H), 7.76 (s, 4H), 7.67-6.4 (d, 2H), 7.38 (dd, 1H), 7.08 (d, 2H), 6.94 (dd, 1H), 5.20-5.11 (m, 0.5H), 4.64-4.52 (m, 2H), 4.42-4.32 (m, 2H), 4.27-4.19 (m, 0.5H), 2.35 (s, 1.5H), 2.34 (s, 1.5H);

MS (ESI) m/e 405 (M+H)⁺;

Anal. calcd for C₂₂H₂₀N₄O₄: C, 65.34; H, 4.98; N, 13.85. Found: C, 64.85 H, 5.36; N, 13.44.

20

Example 105

(⁺)-N-[1-[[[4'-cyano[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide;

- 25 The title compound was made according to the procedures of example 61, but using example 47A in place of example 16B in example 61A.

¹H NMR (300 MHz, d₆-DMSO) δ 9.98 (s, 0.5H), 9.62 (s, 0.5H), 8.31 (s, 0.5H), 8.22 (s, 0.5H), 8.12 (s, 0.5H), 8.05-7.96 (m, 8H), 7.82 (s, 0.5H), 4.55-4.46 (m, 0.5H), 4.07-3.97 (m, 0.5H), 3.70-3.56 (m, 2H), 3.32-3.24 (m, 2H), 2.02-1.88 (m, 0.5H), 1.76-1.64 (m, 0.5H), 1.21-1.18 (m, 6H);

- 30 MS (ESI) m/e 485 (M+H)⁺.

Example 106

(⁺)-N-[1-[[[4-(4-fluorophenoxy)phenyl]sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was made according to the procedures of example 61, but using example 26A in place of example 16B and 4-(4'-fluorooxy)-benzene thiol in place of 4'-thiol-4-biphenyl carbonitrile in example 61A.

¹H NMR (300 MHz, d₆-DMSO) δ 9.66 (s, 0.5H), 9.50 (s, 0.5H), 8.39 (s, 0.5H), 8.35 (s, 0.5H), 8.10 (s, 0.5H), 7.88 (dd, 2H), 7.68 (s, 0.5H), 7.36-7.30 (m, 2H), 7.26-7.20 (m, 2H), 7.15 (d, 2H), 4.88-4.80 (m, 0.5H), 4.51-4.41 (m, 0.5H), 3.70-3.39 (m, 4H), 1.24-1.22 (m, 6H);

MS (ESI) m/e 480 (M+H)⁺;

Anal. calcd for C₂₁H₂₂FN₃O₇S: C, 52.60; H, 4.62; N, 8.76. Found: C, 52.79; H, 4.57; N, 8.68.

Example 107

N-[1-[[4-(4-pyridinyl)phenoxy]methyl]-2-(3,4,4-trimethy-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures of examples 16C and 16E, except substituting 4-(4-pyridinyl)-phenol in place of 4-bromophenol in example 16C. mp: 217-218 °C

¹H NMR (DMSO-d₆): δ 9.53-9.97 (c, 1H), 8.55-8.60 (c, 2H), 8.32 (s, 1/2H), 7.92 (s, 1/2H), 7.77 (s, 1H), 7.75 (s, 1H), 7.65 (s, 1H), 7.64 (s, 1H), 7.01-7.08 (c, 2H), 4.82-4.89 (c, 1/2H), 4.39-4.46 (c, 1/2H), 4.18-4.25 (c, 1H), 4.08-4.17 (c, 1H), 3.71-3.83 (c, 1H), 3.57-3.66 (c, 1H), 2.78 (s, 1.5H), 2.77 (s, 1.5H), 1.27 (s, 3H), 1.26 (s, 3H);

MS (ESI(+)) 413 (M+H), 435 (M+Na), 847 (2M+Na);

Anal. Calcd for: C₂₁H₂₄N₄O₅•0.5H₂O C, 59.84; H, 5.98; N, 13.29. Found: C, 60.18; H, 6.05; N, 13.10.

Example 108

(S)-N-[1-[(4,4-dimethy-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethoxy)]-1,1'-biphenyl]-4-yl]oxy]ethyl]-N-hydroxyformamide

Example 108A

(R)-1-(4-(4'-(trifluoromethoxyphenyl)phenoxy)-3-benzyloxy-2-propanol

A solution of 4-(4'-trifluoromethoxyphenyl)-phenol (1.854g, 7.3 mmol) and (S)-2-(benzyloxymethyl)-oxirane (1.0g, 6.1 mmol) in DMF (15 mL) was treated with potassium carbonate (1.007 g, 7.3 mmol), then stirred at 80° C overnight. The reaction mixture was allowed to cool to 25 °C, poured into water (100 mL) and extracted twice with ethyl acetate (200 mL x 2). The combined organics were washed with sat. aq. NH₄Cl, water, brine, dried (Na₂SO₄), filtered, and concentrated. Purification via flash silica

chromatography eluting with 20 to 25% ethyl acetate: hexane afforded 2.03 g (80% yield) of 108A as a white solid.

Example 108B

A solution of example 108A (1.505 g, 3.6 mmol), di-Boc hydroxylamine (1.007 g, 4.3 mmol), triphenyl phosphine (1.23 g, 4.7 mmol) in THF (15 mL) was treated with diethylazodicarboxylate (0.735 mL, 4.7 mmol) at room temperature, stirred for 1h, then concentrated. The crude was purified by column chromatography eluting with 10% ethyl acetate: hexane to give 1.16 g (50%) of 108B.

Example 108C

A solution of example 108B (248 mg, 0.4 mmol) in THF (3mL) was hydrogenated (H2 balloon) overnight in the presence of 23 mg of 10%pd on carbon. The reaction mixture was filtered, concentrated and purified via silica gel column chromatography eluting with 25% ethyl acetate: hexane to afford 180 mg (85%) of the title compound.

Example 108D

A solution of example 108C (228 mg, 0.42 mmol), 5,5-dimethyl hydantoin (94 mg, 0.73 mmol) and triphenyl phosphine (165 mg, 0.63 mmol) in THF (4 mL) was treated with diethylazodicarboxylate (0.1 mL, 0.63 mmol) added dropwise via syringe. The resulting light yellow solution was stirred at 25 °C for 45 mn, concentrated and purified via silica gel column chromatography eluting with 25% ethyl acetate: hexane to afford 193 mg (71%) of 108D.

Example 108E

(S)-N-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-N-hydroxy amine

A solution of example 108D (191 mg, 0.29 mmol) in methylene chloride (3 mL) was treated with TFA (1.5 mL), added dropwise via syringe. The reaction was stirred at rt for 40 min then concentrated and the residue was partitioned between ethyl acetate and aq. NaHCO₃, the organic extract was washed with brine, dried (Na₂SO₄), filtered, and concentrated to afford 113 mg (86%) of 108E as a white solid.

Example 108F

(S)-N-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-N-hydroxyformamide

The title compound was prepared from 108E following the procedure of example

2F.

MS (ESI) m/e 482 (M+H)⁺.

Example 109

(R)-N-[1-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures of example 108, except using (R)-2-(benzyloxymethyl)-oxirane in place of (S)-2-(benzyloxymethyl)-oxirane.

¹H NMR (300 MHz, d₆-DMSO) δ 9.86 (s, 0.5H), 9.55 (s, 0.5H), 8.39 (s, 0.5H), 8.35 (s, 0.5H), 8.33 (s, 0.5H), 7.93 (s, 0.5H), 7.76-7.73 (m, 2H), 7.64 (d, 2H), 7.42 (d, 2H), 7.02 (dd, 2H), 4.91-4.80 (m, 0.5H), 4.47-4.38 (m, 0.5H), 4.23-4.06 (m, 2H), 3.79-3.50 (m, 2H), 1.27 (s, 1.5H), 1.26 (s, 1.5H);

MS (ESI) m/e 482 (M+H)⁺.

Example 110

N-[1-[[4'-(trifluoromethoxy)][1,1'-biphenyl]-4-yl]oxy]methyl]-3-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)propyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 5, except avoiding the methylation step in example 5B and substituting 4-(4'-trifluoromethoxyphenyl)phenol for 4'-hydroxy-4-biphenylcarbonitrile in example 5F. mp: 197.1-197.9°C;

¹H NMR (300 MHz, DMSO- δ_6) δ ; 1.27 (s, 6H), 1.70-2.00 (m, 2H), 3.35-3.46 (2H), 3.97-4.16 (m, 2.75H), 4.51 (br s, 0.25H), 7.00-7.03 (d, 2H, J=9 Hz), 7.39-7.42 (d, 2H, J=9 Hz), 7.60-7.63 (d, 2H, J=9 Hz), 7.72-7.75 (d, 2H, J=9 Hz), 8.25-8.35 (2H), 9.55 (s, 0.75H), 9.95 (br s, 0.25H);

MS (ESI) m/e 496 (M+H)⁺, 518 (m+Na)⁺, 494 (m-H)⁻, 530 (m+Cl)⁻;

Anal. calcd for C₂₃H₂₄F₃N₃O₆: C, 55.75; H, 4.88; N, 8.48. Found: C, 55.72; H, 5.07; N, 8.59.

Example 111

N-[1-[4-[(4-pyridinylthio)phenoxy]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures of example 23B, except substituting (prepared by the addition of 4-hydroxythiophenol to 4-chloropyridine) for 4-(4'-butyloxyphenyl)-phenol.

¹H NMR (300 MHz, DMSO- δ_6) δ ; 1.258-1.272 (6H), 3.492-3.793 (m, 2H), 4.082-4.248 (m, 2H), 4.437 (m, 0.5H), 3.861 (m, 0.5H), 5.759 (s, 1H), 6.927-6.948 (dd, 2H, J=1.5, 4.8 Hz), 7.063-7.102 (dd, 2H, J=3, 8.7 Hz), 7.529-7.557 (d, 2H, J=8.4 Hz), 7.939 (s, 0.5H), 8.323-8.343 (dd, 2H, J=1.2, 4.8 Hz), 8.391 (s, 0.5H), 9.555 (s, 0.5H), 9.866 (s, 0.5H);

MS (ESI) m/e 431 (M+H)⁺, 453 (m+Na)⁺, 429 (m-H)⁻, 465 (m+Cl)⁻.

Example 112

N-[1-[[[(4-chlorophenoxy)phenyl]sulfonyl]methyl]-3-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)propyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 61, except substituting 4-(4'-chlorophenoxy)benzene thiol for 4'-thiol-4-biphenylcarbonitrile and example 47A for example 16B in example 61A.

¹H NMR (d₆-DMSO) δ 9.94 (s, 0.5H), 9.58 (s, 0.5H), 8.23 (d, 0.5H, J=9.5 Hz), 8.11 (s, 0.5H), 8.05 (d, 0.5H, J=9.2 Hz), 7.89-7.83 (m, 2H), 7.76 (s, 0.5H), 7.54-7.50 (m, 2H), 7.22-7.16 (m, 4H), 4.52-4.41 (m, 0.5H), 4.10-3.92 (m, 0.5H), 3.66-3.37 (m, 2H), 3.31-3.24 (m, 3H), 1.96-1.84 (m, 1H), 1.74-1.62 (m, 1H), 1.28-1.21 (m, 6H);

MS (ESI) 508 (M-H), 510 (M+H), 532 (M+Na).

Example 113

N-[1-[[[(4'-cyano[1,1''-biphenyl]-4-yl)oxy]methyl]-2-(1,6-dihydro-6-oxo-1-pyridazinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures of example 104, except using pyridazinone in place of 6-methyl-3(2H)-pyridazinone.

¹H NMR (d₆-DMSO) δ 9.99 (s, 0.5H), 9.64 (s, 0.5H), 8.28 (s, 0.5H), 7.96-7.83 (m, 5.5H), 7.75-7.71 (m, 2.0H), 7.47-7.41 (m, 1H), 7.07-6.95 (m, 3H), 5.11-5.00 (m, 0.5H), 4.62-4.12 (m, 4.5H);

MS (ESI) 391 (M+H), 413 (M+Na), 389 (M-H);

Anal. Calcd for: C₂₁H₁₈N₄O₄•0.5H₂O C, 63.15; H, 4.79; N, 14.02. Found: C, 63.33; H,

4.66; N, 13.68.

Example 114

N-[1-[[[4'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]oxy]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures of examples 16C and 16E, except substituting 4-(4'-sulfonamidephenyl)-phenol for 4-bromophenol.
mp 203-205 °C;

¹H NMR (DMSO-d₆): δ 9.88 (bs, 1/2H), 9.54 (bs, 1/2H), 8.32 (s, 1/2H), 7.56-8.01 (c, 5 1/2H), 7.34 (s, 1H), 7.00-7.14 (c, 4H), 4.78-4.97 (c, 1/2H), 4.34-4.50 (c, 1/2H), 4.06-4.27 (c, 2H), 3.69-3.85 (c, 1H), 3.57-3.68 (c, 1H), 2.78 (s, 3H), 1.17-1.28 (c, 6H);

13C NMR (DMSO-d₆): δ 176.5, 176.2, 163.1, 158.1, 154.2, 154.1, 128.3, 128.2, 128.0, 127.0, 126.8, 126.2, 115.2, 64.8, 60.7, 36.7, 36.4, 24.2, 21.4;
MS (ESI(+)) 491 (M+H), 508 (M+NH₄), 513 (M+Na).

Example 115

N-[1-[[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

The title compound was prepared following the procedures of example 46, except substituting 4-trifluoromethoxybenzeneboronic acid for 4-butyloxybenzeneboronic in example 46B.

mp 195-197 °C;

¹H NMR, (DMSO-d₆): δ 9.62 (bs, 1H), 8.29-8.43 (c, 1H), 8.10 (s, 1/2H), 7.95-8.05 (c, 4H), 7.92 (d, 1H, J=3 Hz), 7.88 (d, 1H, J=3 Hz), 7.74 (s, 1/2H), 7.54 (s, 1H), 7.49 (s, 1H), 4.87-4.99 (c, 1/2H), 4.50-4.63 (c, 1/2H), 3.43-3.80 (c, 4H), 1.22 (s, 6H);

¹³C NMR (DMSO-d₆): δ 177.2, 177.1, 162.3, 157.1, 155.0, 154.8, 148.7, 144.0, 143.9, 138.0, 137.8, 137.5, 129.2, 128.6, 128.4, 127.9, 127.7, 121.5, 118.4, 57.8, 53.3, 53.0, 51.3, 47.5, 38.8, 38.1, 24.31, 24.30;

MS (ESI(+)) 530 (M+H), 547 (M+NH₄), 552 (M+Na), 1076 (2M+NH₄), 1081 (2M+Na);

HRMS: Calcd: 530.120. Found: 530.1193;

Anal. Calcd for: C₂₂H₂₂F₃N₃O₅S C, 49.90; H, 4.19; N, 7.94; F, 10.76; S, 6.06.

Found: C, 49.58; H, 4.10; N, 7.75; F, 11.04; S, 5.96.

Example 116

N-[1-[4-[(4-pyridinyloxy)phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide

Example 116A

4-[4-(methylsulfonyl)phenoxy]pyridine

A mixture of 4-methylsulfonylphenol (2.93g, 17 mmol) and 4-chloropyridine hydrochloride (2.93 g, 19.5 mmol) was heated at 150° C, resulting in a gradual melt, which was stirred at 150 °C for 4h, then partitioned between ethyl acetate and 1N NaOH. The organic extract was dried over MgSO₄, filtered, and concentrated to 1.3 g of a yellow solid. The solid was recrystallized from ethyl acetate-ether to give 0.81 g of the title compound as a white solid.

Example 116B

N-[1-[4-[(4-pyridinyloxy)phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide

The title compound was prepared following the procedures of examples 75, except substituting example 116A for 71B and acetaldehyde for propionaldehyde.

mp 180-181 °C;

¹H NMR, 400MHz (DMSO-d₆): δ 9.71 (bs, 1H), 8.54 (d, 2H, J=3 Hz), 8.05 (s, 1/2H),

7.97 (d, 2H, J=6 Hz), 7.84 (s, 1/2H), 7.49 (d, 2H, J=6 Hz), 7.03-7.13 (c, 2H),

4.63-4.73 (c, 1/2H), 4.28-4.39 (c, 1/2H), 3.59-3.78 (c, 1H), 3.48 (dd, 1H, J=3,10.5 Hz),

1.20 (dd, 3H, J=4.5, 10.5 Hz);

¹³C NMR (DMSO-d₆): δ 162.62, 162.61, 161.33, 158.33, 158.31, 156.74, 151.77, 135.40,

135.13, 130.74, 130.45, 120.56, 120.34, 113.27, 56.50, 49.69, 45.02, 19.05, 17.71;

MS (ESI(+)) 337 (M+H), 359 (M+Na), 391 (M+Na+MeOH), 695 (2M+Na);

Anal. Calcd for: C₁₅H₁₆N₂O₃S•0.5H₂O: C, 52.16; H, 4.96; N, 8.11; S, 9.28.

Found: C, 52.32; H, 4.78; N, 7.98; S, 9.45.

Example 117

N-[1-[[[4-(4-cyanophenoxy)phenyl]sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 61, except substituting 4-(4'-cyanophenoxy)benzene thiol for 4-thiol-4-biphenylcarbonitrile and example 23A for example 16B, in example 61A.

¹H NMR (300 MHz, d₆-DMSO) δ 9.70 (s, 0.5H), 9.50 (s, 0.5H), 8.39 (s, 0.5H), 8.34 (s, 0.5H), 8.10 (s, 0.5H), 7.98-7.91 (m, 4H), 7.68 (s, 0.5H), 7.37-7.27 (m, 4H), 4.88-4.77 (m, 0.5H), 4.52-4.41 (m, 0.5H), 3.78-3.39 (m, 4H), 1.24-1.22 (m, 6H);

MS (ESI) m/e 487 (M+H)⁺;

Anal. calcd for C₂₂H₂₂N₄O₇S: C, 54.31; H, 4.56. Found: C, 54.17; H, 4.79.

Example 118

N-[1-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]methyl]-3-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)propyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 61, except substituting 4-(4'-trifluoromethoxyphenoxy)benzene thiol for 4'-thiol-4-biphenylcarbonitrile and example 47A for example 16B, in example 61A.

¹H NMR (d₆-DMSO) δ 9.96 (s, 0.5H), 9.60 (s, 0.5H), 8.32 (s, 0.5H), 8.23 (s, 0.5H), 8.11 (s, 0.5H), 7.93-7.86 (m, 2H), 7.75 (s, 0.5H), 7.48 (d, 0.5H, J=8.8 Hz), 7.25 (dd, 4H, J=22.8, 8.8 Hz), 4.53-4.42 (m, 0.5H), 4.04-3.93 (m, 0.5H), 3.65-3.46 (m, 2H), 3.34-3.22 (m, 2H), 2.02-1.62 (m, 2H), 1.26 (s, 3H), 1.23 (s, 3H);

MS (ESI) 560 (M+H), 577 (M+NH₄), 582 (M+Na), 558 (M-H);

Anal. Calcd for: $C_{23}H_{24}N_3O_8SF_3$: C, 49.37; H, 4.32; N, 7.51. Found: C, 49.46; H, 4.23; N, 7.47.

Example 119

N-[1-[[4-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]methyl]-2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-*N*-hydroxyformamide

The title compound was prepared according to the procedures of example 61, except substituting 4-(4'-trifluoromethoxyphenoxy)benzene thiol for 4'-thiol-4-biphenylcarbonitrile in example 61A.

1H NMR (d6-DMSO) δ 9.51 (s, 0.5H), 9.70 (s, 0.5H), 8.09 (s, 0.5H), 7.91 (dd, 2H, $J=8.9$, 3.1 Hz), 7.68 (s, 0.5H), 7.47 (d, 2H, $J=9.2$ Hz), 7.31-7.21 (m, 4H), 4.90-4.78 (m, 0.5H), 4.51-4.40 (m, 0.5H), 3.74-3.40 (m, 4H), 2.76 (d, 3H, $J=1.7$ Hz), 1.27-1.22 (m, 6H); MS (ESI) 558 (M-H), 560 (M+H), 577 (M+NH₄), 582 (M+Na);

Anal. Calcd for: $C_{23}H_{24}N_3O_8SF_3$: C, 49.37; H, 4.32; N, 7.51. Found: C, 49.41; H, 4.29; N, 7.36.

Example 120

(+)-N-hydroxy-N-[1-(3-pyridinyl)-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 75, except substituting 3-pyridine carboxaldehyde for propionaldehyde and 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone (ex. 76A) for 4-(4'-methoxyphenyl)phenyl methyl sulfone in Example 75A.

mp 186.5-188.8 °C;

MS (ESI) m/z 451 (M+H)⁺, 473 (M+Na)⁺, 449 (M-H)⁻;

1H NMR (300 MHz, DMSO- d_6) δ 4.16-4.34 (m, 2H), 5.58 (brs, 0.5H), 5.79 (brs, 0.5H), 7.27-7.32 (dd, 1H, $J=4.8$, 7.8 Hz), 7.78-7.98 (9H), 8.14 (brs, 0.5H), 8.27 (brs, 0.5H), 8.46-8.47 (d+brs 1.5H, $J=4.5$ Hz), 8.60 (brs, 0.5H), 9.70 (brs, 0.5H), 10.14 (brs, 0.5H);

Anal. calcd for $C_{21}H_{17}N_2F_3O_4S$: C, 55.99; H, 3.80; N, 6.21. Found: C, 55.79; H, 3.76; N, 6.18.

Example 121

(+)-N-hydroxy-N-[1-(hydroxymethyl)-2-[[4-(4-chlorophenoxy)phenyl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures described in Examples 77 and 78, except substituting Example 74A for Example 76A.
mp 108.3-110.5 °C;

5 MS (ESI) m/z 403 ($M+NH_4$)⁺, 420 ($M+Cl$)⁻, 384 ($M-H$)⁻;

¹H NMR (300 MHz, DMSO-*d*₆) δ 3.29-3.59 (m, 4H), 3.94-4.06 (m, 0.7H), 4.50-4.60 (m, 0.3H), 4.94-5.01 (m, 1H), 7.17-7.21 (dd, 4H, *J*=3, 8.7 Hz), 7.51-7.54 (d, 2H, *J*=8.7 Hz), 7.76 (s, 0.7H), 7.86-7.90 (2H), 8.12 (s, 0.3H), 9.39 (s, 0.7H), 9.80 (s, 0.3H);

Anal. calcd for C₁₆H₁₆NCIO₆S: C, 49.80; H, 4.18; N, 3.63. Found: C, 49.51; H, 4.31; N,

10 3.46.

Example 122

15 (⁺)-*N*-hydroxy-*N*-[1-methyl-2-[[4'-(trifluoromethyl)][1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures described in Examples 71C-71E, except substituting Example 76A for Example 71A.
mp 174.6-175.2 °C;

20 MS (ESI) m/z 388 ($M+H$)⁺, 410 ($M+Na$)⁺, 386 ($M-H$)⁻, 422 ($M+Cl$)⁻;

¹H NMR (300 MHz, DMSO-*d*₆) δ 1.16-1.24 (dd, 3H, *J*=6.3, 17.7 Hz), 3.49-3.56 (dd, 1H, *J*=4.2, 14.4 Hz), 3.61-3.74 (m, 1H), 4.30-4.43 (m, 0.5H), 4.64-4.78 (m, 0.5H), 7.87-8.07 (9H), 9.48 (brs, 0.5H);

Anal. calcd for C₁₇H₁₆NF₃O₄S: C, 52.71; H, 4.16; N, 3.61. Found: C, 52.74; H, 4.23; N,

25 3.57.

Example 123

30 (⁺)-*N*-hydroxy-*N*-[1-(2-pyridinyl)-2-[[4'-(trifluoromethyl)][1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 75, except substituting 2-pyridine carboxaldehyde for propionaldehyde and 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone (ex. 76A) for 4-(4'-methoxyphenyl)phenyl methyl sulfone in Example 75A.

mp 168.5-168.9 °C;

MS (ESI) m/z 451 (M+H)⁺, 473 (M+Na)⁺, 449 (M-H)⁻, 485 (M+Cl)⁻;

¹H NMR (300 MHz, DMSO-d₆) δ 3.98-4.12 (m, 1H), 4.36-4.42 (d, 1H, J=15.3 Hz), 5.57 (br, 0.5H), 5.89 (br, 0.5H), 7.28-7.33 (m, 1.5H), 7.41-7.44 (d, 0.5H, J=6.9 Hz), 7.73-7.83 (m, 1H), 7.87-7.90 (2H), 7.97-7.80 (m, 6H), 8.25 (s, 1H), 8.45 (br, 1H), 9.69 (s, 0.5H), 10.07 (s, 0.5H);

Anal. calcd for C₂₁H₁₇N₂F₃O₄S: C, 55.99; H, 3.80; N, 6.21. Found: C, 55.88; H, 3.61; N, 6.17.

Example 124

(⁺)-N-[1-[(4,4-dimethyl-2,6-dioxo-1-piperidinyl)methyl]-2-[[4'-(trifluoromethyl)][1,1'-biphenyl]-4-yl]sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared using the following sequence of reactions (i) alkylation of epibromohydrin with 3,3-dimethylglutarimide in the presence of potassium carbonate in methanol (ii) opening the resulting epoxide with 4-bromothiophenol as in Example 2B in the presence of potassium carbonate (iii) alcohol oxidation to the ketone as in Example 2C (iv) coupling the resulting ketone with 4-trifluorobenzene boronic acid, as in Example 46B and (v) converting the resulting ketone to the title compound following the procedures of Examples 46C-D.

mp 185.6-187.3 °C;

MS (APCI) m/z 527 (M+H)⁺, 544 (M+NH₄)⁺, 561 (M+Cl)⁻;

¹H NMR (300 MHz, DMSO-d₆) δ 0.927-0.935 (s+s, 6H), 3.443-3.538 (m, 1H), 3.652-3.784 (m, 2H), 3.884-3.993 (m, 1H), 4.390-4.416 (m, 0.5H), 4.916-4.945 (m, 0.5H), 7.765 (s, 0.5H), 7.882-7.910 (2H), 7.987-8.065 (m, 6.5H), 9.523 (s, 0.5H), 9.660 (s, 0.5H);

Anal. calcd for C₂₄H₂₅N₂F₃O₆S.0.25 hexanes : C, 55.88; H, 5.24; N, 5.11. Found: C, 55.65; H, 5.15; N, 5.02.

Example 125

([±])-N-hydroxy-N-[3-hydroxy-1-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]propyl]formamide

Example 125A

([±])-N-[3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]propyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of Example 75, except substituting 3-*tert*-butyldimethylsilyloxy-propionaldehyde for propionaldehyde and 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone (Example 76A) for 4-(4'-methoxyphenyl)phenyl methyl sulfone in Example 75A.

Example 125B

([±])-N-hydroxy-N-[3-hydroxy-1-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]propyl]formamide

A solution of 125A (488 mg, 0.92 mmol) in THF (20 mL) at 0 °C was treated with TBAF (1.0M/THF, 1.84 mL, 1.84 mmol), stirred at 0 °C for one hour, treated with water, extracted with ethyl acetate, dried (Na₂SO₄), concentrated and triturated sequentially with ethyl ether and dichloromethane to provide 257 mg (67%) of the title compound as an off-white solid.

mp 186.5-188.8 °C;

MS (APCI) m/z 418 (M+H)⁺, 435 (M+NH₄)⁺, 452 (M+Cl)⁻;

¹H NMR (300 MHz, DMSO-*d*₆) δ 1.56-1.82 (m, 2H), 3.51-3.57 (dd, 1H, J=3, 15 Hz), 3.63-3.76 (m, 1H), 4.26-4.38 (m, 0.5H), 4.50-4.51 (br, 0.7H), 4.52-4.53 (m, 0.3H), 7.81-8.09 (9H), 9.48 (br, 0.5H);

Anal. calcd for C₁₈H₁₈NF₃O₅S: C, 51.79; H, 4.34; N, 3.35. Found: C, 51.77; H, 4.50; N, 3.28.

Example 126

09905242.071601
(⁺)-N-hydroxy-N-[1-(methoxymethyl)-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide

Example 126A

1-methoxy-3-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]-2-propanone

A solution of 4-(4'-(trifluoromethyl)phenyl)phenyl methyl sulfone (1.0 g, 3.33 mmol) in THF (50 mL) at -78 °C was treated with n-butyllithium (2.5M/hexanes, 1.4 mL, 3.50 mmol), stirred at -78 °C for 1.5 hours and then treated with ethyl methoxyacetate (0.78 mL, 6.66 mmol), stirred at -78 °C for three hours, treated with saturated NH₄Cl solution, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na₂SO₄), concentrated and purified on silica gel with 30-50% ethyl acetate/hexanes to provide 902 mg (73%) of the title compound as a white solid. MS (APCI) m/z 390 (M+NH₄)⁺, 371 (M-H)⁻, 470 (M+Cl)⁻.

Example 126B

(⁺)-1-methoxy-3-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]-2-propanol

A suspension of Example 126A (850 mg, 2.28 mmol) in ethanol (100 mL) at ambient temperature was treated with sodium borohydride (103 mg, 2.74 mmol), stirred for 30 minutes, treated with water, extracted with ethyl acetate, dried (Na₂SO₄) and concentrated to provide 820 mg (96%) of the title compound as a white solid. MS (APCI) m/z 392 (M+NH₄)⁺, 409 (M+Cl)⁻.

Example 126C

(⁺)-N-hydroxy-N-[1-(methoxymethyl)-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide

Example 126B was converted to the title compound following the procedures of Examples 75C and 75D.

mp 175.3-176.3 °C;

MS (ESI) m/z 418 (M+H)⁺, 435 (M+NH₄)⁺, 440 (M+Na)⁺, 416 (M-H)⁻;

¹H NMR (300 MHz, DMSO-d₆) δ 3.17 (s, 1.5H), 3.21 (s, 1.5H), 3.41-3.51 (m, 2H), 3.63-3.68 (m, 1H), 4.28 (m, 0.5H), 4.80 (m, 0.5H), 7.87-7.90 (2.5H), 7.98-8.03 (6H), 8.14 (s, 0.5H), 9.54 (br s, 0.5H), 9.94 (0.5H);

Anal. calcd for C₁₈H₁₈NF₃O₅S: C, 51.79; H, 4.34; N, 3.35. Found: C, 51.57; H, 4.50; N, 3.31.

Example 127

([±])-N-[1-(1,3-benzodioxol-5-yl)-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of Example 75, except substituting piperonal for propionaldehyde and 4-(4'-trifluoromethylphenyl)-phenyl methyl sulfone (ex. 76A) for 4-(4'-methoxyphenyl)phenyl methyl sulfone in Example 75A.

mp 159.5-160.5 °C;

MS (ESI) m/z 516 (M+Na)⁺, 492 (M-H)⁻, 528 (M+Cl)⁻;

¹H NMR (300 MHz, DMSO-d₆) δ 4.02-4.18 (br, 2H), 5.30-5.40 (br, 0.5H), 5.60-5.70 (br, 0.5H), 5.85 (s, 0.5H), 5.92 (s, 0.5H), 6.77-6.93 (3H), 7.88-7.98 (m, 8H), 8.09-8.10 (br, 0.5H), 8.19-8.22 (br, 0.5H), 9.52-9.64 (br, 0.5H), 9.94-10.10 (br, 0.5H);

Anal. calcd for C₂₃H₁₈N₂F₃O₆S: C, 55.98; H, 3.67; N, 2.83. Found: C, 55.86; H, 3.65; N, 2.79.

Example 128

([±])-N-hydroxy-N-[4-hydroxy-1-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]methyl]butyl]formamide

The title compound was prepared according to the procedures of Example 125, except substituting 4-*tert*-butyldimethylsilyloxybutanaldehyde for 3-*tert*-butyldimethylsilyloxypropionaldehyde.

mp 138.9-140.3 °C;

MS (ESI) m/z 432 (M+H)⁺, 454 (M+Na)⁺, 466 (M+Cl)⁻;

¹H NMR (300 MHz, DMSO-d₆) δ 1.22-1.36 (m, 2H), 1.44-1.66 (m, 2H), 3.47-3.54 (1H), 3.62-3.71 (m, 1H), 4.10-4.20 (m, 0.6H), 4.39-4.44 (m, 1H), 4.52-4.62 (m, 0.4H), 7.88-8.13 (10H), 9.47 (s, 0.6H), 9.85 (s, 0.4H);

Anal. calcd for C₁₉H₂₀N₂F₃O₅S: C, 52.89; H, 4.67; N, 3.24. Found: C, 53.26; H, 5.00; N,

3.25.

Example 129

([±])-N-hydroxy-N-[1-[4-(methoxymethoxy)phenyl]-2-[[4'-(trifluoromethyl)]1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 75, except substituting 4-(methoxymethoxy)benzaldehyde for propionaldehyde and 4-(4'-trifluoromethylphenyl)-phenyl methyl sulfone (ex. 76A) for 4-(4'-methoxyphenyl)-phenyl methyl sulfone in Example 75A.

mp 137.1-138.5 °C;

MS (ESI) m/z 527 (M+NH₄)⁺, 508 (M-H)⁻, 544 (M+Cl)⁻;

¹H NMR (300 MHz, DMSO-d₆) δ 3.28 (s, 3H), 4.00-4.20 (2H), 5.12 (s, 2H), 5.40 (br, 0.5H), 5.60 (br, 0.5H), 6.88-6.91 (d, 2H, J=8.7 Hz), 7.18-7.32 (m, 2H), 7.87-7.99 (m, 8H), 8.09 (br, 0.5H), 8.22 (br, 0.5H), 9.58 (s, 0.5H), 10.02 (s, 0.5H);

Anal. calcd for C₂₄H₂₂NF₃O₆S: C, 56.57; H, 4.35; N, 2.74. Found: C, 56.59; H, 4.50; N, 2.70.

Example 130

([±])-N-hydroxy-N-[1-(1-methyl-1H-pyrrol-2-yl)-2-[[4-(4-(trifluoromethoxy)phenoxy)phenyl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 75, except substituting 2-N-Methylpyrrole carboxaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in Example 75A.

MS (ESI) M-H (483);

¹H NMR (300 MHz, DMSO-d₆) δ 9.90 (s, 1H), 9.51 (s, 1H), 8.07 (s, 1H), 7.87-7.83 (d, 2H, J=8.9 Hz), 7.49-7.46 (d, 2H, J=8.4 Hz), 7.27-7.24 (d, 2H, J=8.8 Hz), 7.17-7.14 (d, 2H,

J=8.8 Hz), 6.65 (s, 1H), 6.02 (s, 1H), 5.85-5.79 (m, 1H), 4.04-3.87 (mm, 2H), 3.53-3.44 (m, 3H);
Anal. calcd for C₂₁H₁₉N₂O₆SF₃: C, 52.06; H, 3.95; N, 5.78. Found: C, 52.42; H, 4.12; N, 5.48.

5

Example 131

([±])-N-hydroxy-N-[1-phenyl-2-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

10 The title compound was prepared according to the procedures of Example 75, except substituting benzaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in Example 75A.

MS (ESI) M-H (480);

15 ¹H NMR (300 MHz, DMSO-d₆) δ 10.06 (s, 0.5H), 9.96 (s, 0.5H), 8.18-8.11 (m, 1H), 7.87-7.85 (m, 2H), 7.50-7.47 (d, 2H, J=8.8 Hz), 7.30-7.24 (m, 5H), 7.15-7.13 (d, 2H, J=8.5 Hz), 5.78 (s, 0.5H), 5.41 (s, 0.5H), 4.24-4.04 (mm, 3H);

Anal. calcd for C₂₂H₁₈NO₆SF₃: C, 54.88; H, 3.76; N, 2.90. Found: C, 54.58; H, 3.89; N, 2.96.

20

Example 132

([±])-N-hydroxy-N-[1-(2-thienyl)-2-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

25 The title compound was prepared according to the procedures of Example 75, except substituting 2-thiophene carboxaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in Example 75A.

MS (ESI) M-H (486);

30 ¹H NMR (300 MHz, DMSO-d₆) δ 10.15 (s, 0.5H), 9.75 (s, 0.5H), 8.16-8.12 (m, 1H), 7.88-7.85 (d, 2H, J=8.1 Hz), 7.50-7.47 (m, 2H), 7.29-7.25 (d, 2H, J=8.2 Hz), 7.17-7.14 (d, 2H, J=8.8 Hz), 7.08-7.04 (m, 1H), 6.95-6.92 (m, 1H), 5.92 (s, 0.5H), 5.76 (m, 0.5H), 4.05-4.00 (m, 3H);

Anal. calcd for C₂₀H₁₆NO₆S₂F₃: C, 49.27; H, 3.30; N, 2.87. Found: C, 49.01; H, 3.24; N, 2.75.

Example 133

([±])-N-[1-(2-furanyl)-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of Example 75, except substituting 2-furyl carboxaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in Example 75A.

MS (ESI) M-H (470);

¹H NMR (300 MHz, DMSO-d₆) δ 10.03 (s, 0.5H), 9.60 (s, 0.5H), 8.14 (s, 1H), 7.90-7.89 (m, 2H), 7.57 (s, 1H), 7.49-7.46 (d, 2H, J=8.5 Hz), 7.29-7.25 (d, 2H, J=8.5 Hz), 7.19-7.16 (d, 8.5H), 6.41 (s, 1H), 6.39 (s, 1H), 4.04-4.00 (m, 3H);

Anal. calcd for C₂₀H₁₆NO₇SF₃: C, 50.95; H, 3.42; N, 2.97. Found: C, 51.25; H, 3.70; N, 2.99.

Example 134

([±])-N-[1-(5,5-dimethyl-2,4-dioxo-3-oxazolidinyl)-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]-N-hydroxyformamide

Example 134A

1-bromo-3-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]-2-propanone

The title compound was prepared from 3-(4-(4'-trifluoromethoxyphenyl)-phenoxy)propan[1,2]oxirane using the procedure described in Example 47A.

Example 134B

([±])-N-[1-(5,5-dimethyl-2,4-dioxo-3-oxazolidinyl)-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]-N-hydroxyformamide

Example 134B was converted to the title compound by first reacting with 5,5-dimethylloxazolidinine-2,4-dione as in Example 3C, then applying the sequence of reactions described in Examples 2D, 2E and 2F.

¹H NMR (300 MHz, DMSO-d₆) δ 10.09 (s, 0.5H), 9.71 (s, 0.5H), 8.34 (s, 0.5H), 7.98 (s, 0.5H), 7.76-7.73 (d, 2H, J=8.8 Hz), 7.65-7.63 (d, 2H, J=8.5 Hz), 7.43-7.40 (d, 2H, J=8.8 Hz), 7.05-7.02 (d, 2H, J=8.8 Hz), 4.90-4.88 (m, 0.5H), 4.44-4.40 (m, 0.5H), 4.22-4.15 (m, 2H), 3.86-3.68 (m, 1H), 3.66-3.59 (m, 1H), 1.49 (s, 6H);

Anal. calcd for C₂₂H₂₁N₂O₇F₃·0.25 ethyl acetate; C, 54.76; H, 4.59; N, 5.55. Found: C, 54.91; H, 4.49; N, 5.44.

Example 135

(⁺)-N-hydroxy-N-[1-(methoxymethyl)-2-[[4-(4-(trifluoromethoxy)phenoxy)phenyl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 126, except substituting 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

MS (ESI-) 448 (M-H);

¹H NMR (300 MHz, DMSO-d₆) δ 3.20 (s, 3H), 3.23-3.45 (m, 3H), 3.52-3.65 (m, 1H), 4.16-4.27 (m, 0.5H), 4.70-5.02 (m, 0.5H), 7.21 (dd, 2H, J=3,9 Hz), 7.28 (dd, 2H, J=6,9 Hz), 7.47 (d, 2H, J=9 Hz), 7.81 (s, 0.5H), 7.90 (dd, 2H, J=3,9 Hz), 8.12 (s, 0.5H), 9.56 (bs, 0.5H), 9.91 (bs, 0.5H);

Anal. calcd for C₁₈H₁₈NO₇SF₃·0.25 ethyl acetate; C, 48.40; H, 4.27; N, 2.97. Found: C, 48.61; H, 4.33; N, 3.06.

Example 136

(S)-N-hydroxy-N-[1-[(phenylmethoxy)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]formamide

The title compound was prepared from Example 108B following the procedures of Examples 108E and 108F.

MS (ESI-) 460 (M-H);

¹H NMR (300 MHz, DMSO-d₆) δ 3.58-3.73 (m, 2H), 4.0-4.2 (m, 2H), 4.28-4.35 (m, 0.5H), 4.55 (s, 2H), 4.8-4.9 (m, 0.5H), 7.03 (d, 2H, J=9 Hz), 7.25-7.38 (m, 5H), 7.43 (d, 2H, J=9 Hz), 7.63 (d, 2H, J=9 Hz), 7.75 (d, 2H, J=9 Hz), 8.06 (s, 0.5H), 8.42 (s, 0.5H), 9.62 (s, 0.5H), 10.03 (s, 0.5H);

- 5 Anal. calcd for C₂₄H₂₂F₃NO₅: C, 62.47; H, 4.80; N, 3.03. Found: C, 62.29; H, 5.03; N, 2.92.

Example 137

10 (S)-N-hydroxy-N-[1-(hydroxymethyl)-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxyethyl]formamide

The title compound was prepared from Example 108B following the procedures of Examples 108C, 108E and 108F.

MS (ESI-) 370 (M-H);

- 15 ¹H NMR (300 MHz, DMSO-d₆) δ 3.45-3.53 (m, 2H), 3.95-4.20 (m, 2.5H), 4.55-4.68 (m, 0.5H), 4.90-4.98 (m, 1H), 7.05 (d, 2H, J=9 Hz), 7.42 (d, 9H), 7.64 (d, 2H, J=9 Hz), 7.75 (d, 2H, J=9 Hz), 7.98 (s, 0.5H), 8.39 (s, 0.5H), 9.47 (s, 0.5H), 9.89 (s, 0.5H);

Anal. calcd for C₁₇H₁₆F₃NO₅: C, 54.99; H, 4.34; N, 3.77. Found: C, 54.77; H, 4.57; N, 3.54.

20

Example 138

(±)-N-hydroxy-N-[1-(hydroxymethyl)-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]formamide

- 25 The title compound was prepared according to the procedures of Example 125, except substituting t-butyltrimethylsilyloxy-acetaldehyde for 3-tert-butyltrimethylsilyloxy-propionaldehyde and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

mp 115-117 °C;

- 30 MS (ESI+) 436 (M+H), 453 (M+NH₄), 458 (M+Na);

¹H NMR (300 MHz, DMSO-d₆) δ 3.30-3.62 (m, 4H), 3.93-4.03 (m, 0.5H), 4.51-4.61 (m, 0.5H), 4.95-5.06 (m, 1H), 7.22 (d, 2H, J=9.0 Hz), 7.25-7.32 (m, 2H), 7.48 (d, 2H, J=9.0 Hz), 7.76 (s, 0.5H), 7.86-7.94 (m, 2H), 8.13 (s, 0.5H), 9.41 (bs, 0.5H), 9.82 (bs, 0.5H);

Anal. calcd for C₁₇H₁₆NO₇SF₃: C, 46.89; H, 3.70; N, 3.21. Found: C, 46.65; H, 3.71; N, 3.14.

Example 139

[S-(R*,S*)]-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)-phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide

Example 139A and 139B

[S-(R*,S*)]-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)-phenoxy]phenyl]sulfonyl]ethyl]hydroxylamine

139B

[S-(R*,R*)]-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)-phenoxy]phenyl]sulfonyl]ethyl]hydroxylamine

The title compounds were prepared as a diastereomeric mixture according to the procedures of Examples 75A, 75B and 75C, except substituting (R)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenoxy)-phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in Example 75A. The two distereomers were separated via silica gel chromatography to give Example 139A and Example 139B.

Example 139C

[S-(R*,S*)]-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)-phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide

Example 139A was converted to the title compound following the formylation procedure described in Example 1E.

mp 149-150 °C;

MS (ESI+) 506 (M+H), 523 (M+NH₄), 528 (M+Na);

¹H NMR (300 MHz, DMSO-d₆) δ 1.04 (s, 1.5H), 1.13 (s, 1.5H), 1.20 (s, 1.5H), 1.23 (s, 1.5H), 3.57-4.11 (m, 5.5H), 4.39 (t, 0.5H, J=9.80 Hz), 7.19-7.30 (m, 4H), 7.49 (d, 2H, J=8.70 Hz), 7.86-7.97 (m, 2.5H), 8.15 (s, 0.5H), 9.71 (bs, 0.5H), 10.20 (s, 0.5H);

Anal. calcd for C₂₁H₂₂NO₈SF₃: C, 49.90; H, 4.38; N, 2.77. Found: C, 49.90; H, 4.35; N, 2.52.

Example 140

[S-(R*,R*)]-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide

Example 139B was converted to the title compound following the formylation procedure described in Example 1E.

mp 127-128 °C;

MS (ESI+) 506 (M+H), 523 (M+NH₄), 528 (M+Na);

¹H NMR (300 MHz, DMSO-d₆) δ 1.21 (s, 1.5H), 1.23 (s, 1.5H), 1.26 (s, 1.5H), 1.30 (s, 1.5H), 3.28-3.40 (m, 1H), 3.61-3.73 (m, 2H), 3.92-4.14 (m, 2.5H), 4.56 (t, 0.5H, J=8.25 Hz), 7.20-7.31 (m, 4H), 7.48 (d, 2H, J=8.70 Hz), 7.81 (s, 0.5H), 7.92 (t, 2H, J=9.0 Hz), 8.13 (s, 0.5H), 9.63 (bs, 0.5H), 10.01 (bs, 0.5H);

Anal. calcd for C₂₁H₂₂NO₈SF₃: C, 49.90; H, 4.38; N, 2.77. Found: C, 49.96; H, 4.46; N, 2.76.

Example 141

[S-(R*,R*)]-N-[(2,3-dihydroxy)-1-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]-sulfonyl]methyl]propyl]-N-hydroxyformamide

Example 141A

[S-(R*,R*)]-3-(hydroxyamino)-4-[[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-1,2-butanediol

Example 139B (9.6 gm, 20 mmol) was dissolved in THF (300 mL) and treated with 3N HCl (40 mL) dropwise, and the clear solution was stirred at 45 °C for 1 hr. The reaction mixture was neutralized with a slow addition of NaHCO₃ solution and extracted with ether. The organic layer was dried with MgSO₄ and concentrated to white solid. Recrystallization from CH₂Cl₂ afforded pure title compound as a white powder (6.94 gm, 79%).

MS (ESI+) 439 (M+H).

Example 141B[S-(R*,R*)]-N-[(2,3-dihydroxy)-1-[[[4-[4-(trifluoromethoxy)phenoxy]phenyl]-sulfonyl]methyl]propyl]-N-hydroxyformamide

Example 141A was converted to the title compound following the formylation procedure described in Example 1E.

mp 137-138 °C;

MS (ESI+) 466 (M+H), 483 (M+NH₄), 488 (M+Na);

¹H NMR (300 MHz, DMSO-d₆) δ 3.30-3.60 (m, 3H), 3.65-3.78 (m, 1H), 3.90-3.99 (m, 0.5H), 4.53-4.62 (m, 0.5H), 4.78 (bs, 1H), 4.94 (bs, 1H), 7.21 (d, 2H, J=9.0 Hz), 7.25-7.32 (m, 2H), 7.47 (d, 2H, J=8.60 Hz), 7.70 (s, 0.5H), 7.84-7.92 (m, 2H), 8.09 (s, 0.5H), 9.30 (bs, 0.5H), 9.65 (bs, 0.5H);

Anal. calcd for C₁₈H₁₈NO₈SF₃: C, 46.45; H, 3.89; N, 3.00. Found: C, 46.29; H, 3.88; N, 2.91;

[α]_D²⁰=+4.2° (MeOH).

Example 142

(+)-N-[1-[(dimethylamino)methyl]-2-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]-sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of Example 126, except substituting 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone and *N,N*-dimethylglycine ethyl ester for ethyl methoxyacetate.

MS (ESI+) 463 (M+H), 485 (M+Na);

¹H NMR (300 MHz, DMSO-d₆) δ 2.04 (s, 3H), 2.10 (s, 3H), 2.21-2.39 (m, 2H), 3.40-3.48 (m, 1H), 3.53-3.63 (m, 1H), 4.05-4.17 (m, 0.5H), 4.62-4.72 (m, 0.5H), 7.19-7.30 (m, 4H), 7.47 (d, 2H, J=9.0 Hz), 7.86 (s, 0.5H), 7.87-7.94 (m, 2H), 8.10 (s, 0.5H), 9.45 (bs, 0.5H), 9.85 (bs, 0.5H);

Anal. calcd for C₁₉H₂₁N₂O₆F₃S: C, 49.34; H, 4.57; N, 6.05. Found: C, 49.12; H, 4.72; N, 6.04.

Example 143

[S-(R*,R*)]-N-[2-[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]-1-(2,2-dimethyl-1,3-dioxol-4-yl)ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures described for Examples 139 and 140, starting with 4-(4'-chlorophenyl)phenyl methyl sulfone and (R)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde.

MS (ESI+) 440 (M+H), 457 (M+NH₄);

¹H NMR (300 MHz, DMSO-d₆) δ 1.20 (s, 1.5H), 1.22 (s, 1.5H), 1.26 (s, 1.5H), 2.30 (s, 1.5H), 3.32-3.40 (m, 1H), 3.62-3.78 (m, 2H), 3.93-4.15 (m, 2.5H), 4.64 (t, 0.5H, J=8.4 Hz), 7.58 (d, 2H, J=8.4 Hz), 7.77-7.83 (m, 2H), 7.89 (s, 0.5H), 7.93-8.02 (m, 4H), 8.13 (s, 0.5H), 9.62 (bs, 0.5H), 9.97 (bs, 0.5H);

Anal. calcd for C₂₀H₂₂NO₆SCl: C, 54.60; H, 5.04; N, 3.18. Found: C, 54.48; H, 5.30; N, 3.13.

Example 144

([±])-N-[1-[(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures described in Example 134, except substituting saccharin for 5,5-dimethyloxazolidinine-2,4-dione.

MS (ESI-) 535 (M-1);

¹H NMR (300 MHz, DMSO-d₆) δ 3.9-4.2 (m, 2H), 4.2-4.3 (m, 2H), 4.45-4.55 (m, 0.5H), 5.0-5.1 (m, 0.5H), 7.0-7.1 (m, 2H), 7.42 (d, 2H, J=8.4 Hz), 7.64 (d, 2H, J=8.4 Hz), 7.74 (d, 2H, J=9.0 Hz), 8.0-8.2 (m, 3.5H), 8.3-8.4 (m, 1.5H), 9.78 (s, 0.5H), 10.14 (s, 0.5H);

Anal. calcd for C₂₄H₁₉F₃N₂O₇S: C, 53.73; H, 3.56; N, 5.22. Found: C, 53.81; H, 3.78; N, 5.07.

Example 145

[R-(R*,R*)]-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)-phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide

Example 145A and 145B

[R-(R*,R*)]-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]hydroxylamine

145B

[R-(S*,R*)]-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]hydroxylamine

The title compounds were prepared as a diastereomeric mixture according to the procedures of Examples 126A, 126B, 75A and 75B and 75C, starting with 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone and methyl (S)-2,2-dimethyl-1,3-dioxolane-4-carboxylate. The two diastereomers were separated via silica gel chromatography to give

Example 145A and Example 145B.

Example 145C

[R-(R*,R*)]-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)-
phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide

Example 145A was converted to the title compound following the formylation procedure described in Example 1E.

MS (ESI+) 506 (M+1), 523 (M+18);

¹H NMR (300 MHz, DMSO-d₆) δ 1.21 (s, 1.5H), 1.23 (s, 1.5H), 1.26 (s, 1.5H), 1.30 (s, 1.5H), 3.3-3.4 (m, 1H), 3.60-3.75 (m, 2H), 3.9-4.1 (m, 2.5H), 4.5-4.6 (m, 0.5H), 7.2-7.3 (m, 4H), 7.48 (d, 2H, J=8.7 Hz), 7.81 (s, 0.5H), 7.85-7.95 (m, 2H), 8.13 (s, 0.5H), 9.63 (br s, 0.5H), 10.0 (br s, 0.5H);

Anal. calcd for C₂₁H₂₂F₃NO₈S: C, 49.90; H, 4.38; N, 2.77. Found: C, 49.90; H, 4.51; N, 2.66.

Example 146

[R-(S*,R*)]-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)-
phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide

Example 145B was converted to the title compound following the formylation procedure described in Example 1E.

MS (ESI+) 506 (M+H), 523 (M+18);

¹H NMR (300 MHz, DMSO-d₆) δ 1.05 (s, 1.5H), 1.14 (s, 1.5H), 1.20 (s, 1.5H), 1.23 (s, 1.5H), 3.3-3.4 (m, 1H), 3.5-4.1 (m, 4.5H), 4.3-4.4 (m, 0.5H), 7.2-7.3 (m, 4H), 7.48 (d, 2H), 7.8-8.0 (m, 2.5H), 8.15 (s, 0.5H), 9.68 (br s, 0.5H), 10.10 (br s, 0.5H).

Example 147

[S-(R*,R*)]-N-[1-(2,2-diethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)phenoxy]-
phenyl]sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures described for Examples 139 and 140, except substituting (R)-2,2-diethyl-1,3-dioxolane-4-carboxaldehyde for (R)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde.

MS (ESI+) 534 (M+H), 551 (M+18);

¹H NMR (300 MHz, DMSO-d₆) δ 0.7-0.8 (m, 6H), 1.4-1.6 (m, 4H), 3.2-3.3 (m, 1H), 3.45-3.55 (m, 1H), 3.69 (dd, 1H, J=8.7, 15.6 Hz), 3.95-4.15 (m, 2.5H), 4.5-4.6 (m, 0.5H), 7.2-7.3 (m, 4H), 7.47 (d, 2H, J=8.4 Hz), 7.81 (s, 0.5H), 7.85-7.95 (m, 2H), 8.14 (s, 0.5H), 9.66 (br s, 0.5H), 10.11 (br s, 0.5H);

Anal. calcd for C₂₃H₂₆NO₈SF₃: C, 51.77; H, 4.91; N, 2.62. Found: C, 51.98; H, 5.12; N, 2.63.

Example 148

(⁺)-N-hydroxy-N-[1-(hydroxymethyl)-2-[[4'-(methylsulfonyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 125, except substituting *tert*-butyldimethylsilyloxy-acetaldehyde for 3-*tert*-butyldimethylsilyloxy-propionaldehyde and 4-(4'-methylsulfonylphenyl)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

mp 165-167 °C;

MS (ESI(-)) 412 (M-H), 825 (2M-H), 847 (2M+Na-2H);

¹H NMR (300 MHz, DMSO-d₆): δ 8.23 (s, 1/2H), 7.97-8.13 (m, 9H), 7.93 (s, 1/2H), 4.75-4.84 (m, 1H), 4.17-4.35 (m, 1H), 3.57-3.84 (m, 3H), 3.41-3.53 (m, 1H), 3.18 (s, 3H);

HRMS: calc: 414.0681, Found: 414.0668;

Anal. calcd for C₁₇H₁₉NO₇S₂: C, 49.38; H, 4.63; N, 3.38; S, 15.50. Found: C, 34.24; H, 3.47; N, 2.32; S, 14.61.

Example 149

(⁺)-N-[1-[[4-[(1,3-benzodioxol-5-yl)phenyl]sulfonyl]methyl]-2-hydroxyethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of Example 125, except substituting *tert*-butyldimethylsilyloxyacetaldehyde for 3-*tert*-butyldimethyl-

silyloxypropionaldehyde and 4-(3',4'-methylenedioxyphenyl)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

mp 160-161 °C;

MS (APCI) 380 (M+H), 397 (M+NH₄);

- 5 ¹H NMR (300 MHz, DMSO-d₆): δ 9.42-9.83 (m, 1H), 8.19 (s, 1/2H), 7.85-8.00 (m, 4.5H), 7.49 (s, 1H), 7.41 (d, 1H, J=8 Hz), 7.08 (d, 1H, J=8 Hz), 6.13 (s, 2H), 4.96-5.27 (m, 1H), 4.52-4.62 (m, 1/2H), 4.04-4.14 (m, 1/2H), 3.60-3.70 (m, 2H), 3.38-3.46 (m, 2H);
Anal. calcd for C₁₇H₁₇NO₇S: C, 53.82; H, 4.51; N, 3.69; S, 8.45. Found: C, 53.49; H, 4.54; N, 3.58; S, 8.32.

10

Example 150

([±])-N-hydroxy-N-[1-(hydroxymethyl)-2-[[4'-(methylthio)][1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide

- 15 The title compound was prepared according to the procedures of Example 125, except substituting *tert*-butyldimethylsilyloxyacetaldehyde for 3-*tert*-butyldimethylsilyloxypropionaldehyde and 4-(4'-thiomethylphenyl)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

mp 161-162 °C;

- 20 MS (DCI): 382 (M+H), 399 (M+NH₄);

¹H NMR (300 MHz, DMSO-d₆) δ 9.77-10.05 (m, 1/2H), 9.27-9.68 (m, 1/2H), 8.15 (s, 1/2H), 7.89-7.99 (m, 4H), 7.84 (s, 1/2H), 7.72 (s, 1H), 7.70 (s, 1H), 7.58 (s, 1H), 7.56 (s, 1H), 4.98-5.12 (m, 1H), 4.58-4.70 (m, 1/2H), 4.01-4.10 (m, 1/2H), 3.57-3.67 (m, 1.5H), 3.35-3.44 (m, 2H), 3.09-3.19 (m, 1/2H);

- 25 HRMS: calc:382.0783. Found:382.0784;

Anal. calcd for C₁₇H₁₉NO₅S₂·0.25 C₄H₈O₂: C, 53.58; H, 5.25; N, 3.47; S, 15.90. Found: C, 53.77; H, 5.50; N, 3.63; S, 16.02.

Example 151

- 30 ([±])-N-hydroxy-N-[1-(hydroxymethyl)-2-[[4'-(trifluoromethoxy)][1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 125, except substituting *tert*-butyldimethylsilyloxyacetaldehyde for 3- *tert*-butyldimethylsilyloxypropionaldehyde and 4-(4'-trifluoromethoxyphenyl)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

mp 167-168 °C;

MS (APCI) 420 (M+H), 437 (M+NH₄);

¹H NMR (300 MHz, DMSO-d₆): δ 9.85-9.98 (m, 1/2H), 9.41-9.58 (m, 1/2H), 8.18 (s, 1/2H), 7.98-8.07 (m, 3.5H), 7.86-7.97 (m, 3H), 7.56 (s, 1H), 7.53 (s, 1H), 5.03-5.14 (m, 1H), 4.62-4.73 (m, 1H), 4.06-4.17 (m, 1H), 3.64-3.74 (m, 1H), 3.40-3.47 (m, 2H);

HRMS: calc: 420.0729. Found: 420.0722;

Anal. calcd for C₁₇H₁₆F₃NO₆S: C, 48.68; H, 3.84; F, 13.59; N, 3.33; S, 7.64. Found: C, 48.54; H, 4.00; F, 13.67; N, 3.20; S, 7.95.

Example 152

(⁺)-N-hydroxy-N-[1-(hydroxymethyl)-2-[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 125, except substituting *tert*-butyldimethylsilyloxyacetaldehyde for 3- *tert*-butyldimethylsilyloxypropionaldehyde and 4-(4'-chlorophenyl)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

mp 153-154 °C;

MS (ESI(+)) 370 (M+H), 387 (M+NH₄), 392 (M+Na);

¹H NMR (300 MHz, DMSO-d₆): δ 9.34-9.92 (m, 1H), 8.19 (s, 1/2H), 7.95-8.09 (m, 4H), 7.78-7.93 (m, 2.5H), 7.56-7.68 (m, 2H), 4.94-5.21 (m, 1H), 4.62-4.73 (m, 1H), 4.05-4.16 (m, 1H), 3.62-3.74 (m, 2H), 3.52-3.56 (m, 1H);

HRMS: calc: 370.0516. Found: 370.0526;

Anal. calcd for C₁₆H₁₆ClNO₅S·0.25 H₂O: C, 51.33; H, 4.44; Cl, 9.47; N, 3.74; S, 8.56. Found: C, 51.30; H, 4.37; Cl, 9.33; N, 3.72; S, 8.43.

Example 153

([±])-N-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-(4-trifluoromethyl)phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of Example 61, except substituting 4-(4'-trifluoromethylphenoxy)benzenethiol in place of 4'-thiol-4-biphenylcarbonitrile in Example 61A.

mp 141-143 °C;

MS (ESI(+)) 544 (M+H), 561 (M+NH₄), 566 (M+Na), 1104 (2M+N H₄), 1109 (2M+Na);

¹H NMR (300 MHz, DMSO-d₆): δ 9.78 (bs, 1/2H), 9.58 (bs, 1/2H), 8.15 (s, 1/2H), 7.96-8.03 (m, 2H), 7.84-7.90 (m, 2H), 7.74 (s, 1/2H), 7.34-7.41 (m, 4H), 4.86-4.95 (m, 1/2H), 4.49-4.58 (m, 1/2H), 4.10 (s, 1/2H), 3.50-3.82 (m, 3.5H), 2.82 (s, 3H), 1.36-1.44 (m, 6H);

Anal. calcd for C₂₃H₂₄F₃N₃O₇S·0.25 C₄H₈O₂: C, 50.97; H, 4.63; N, 7.43; S, 5.66;

Found: C, 50.75; H, 4.73; N, 7.27; S, 5.60.;

Example 154

(±)-N-hydroxy-N-[1-(hydroxymethyl)-2-[[[4-(methylsulfonyl)phenoxy]phenyl]sulfonyl]ethyl]formamide

Example 154A

(±)-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-[4-[4-(methylthio)phenoxy]phenyl]thio]-2-propanone

Reaction of 4-(4'-methylsulfonephenoxy)benzenethiol with 3-(*tert*-butyldimethylsilyloxy)propan-[1,2]oxirane followed by Dess Martin oxidation as described in Examples 2B and 2C afforded the title compound.

Example 154B

(±)-N-hydroxy-N-[1-(hydroxymethyl)-2-[[[4-(methylsulfonyl)phenoxy]phenyl]sulfonyl]ethyl]formamide

The title compound was prepared from Example 154A, following the procedures described in Examples 61B and 61C.

MS (ESI) 430 (M+H), 447 (M+NH₄), 452 (M+Na), 428 (M-H);

¹H NMR (300 MHz, DMSO-d₆) δ 9.84 (br, 0.5H), 9.40 (br, 0.5H), 8.12 (s, 0.5H), 8.02-7.91 (m, 4H), 7.75 (s, 0.5H), 7.38-7.29 (m, 4H), 5.09-4.94 (m, 1H), 4.61-4.52 (m, 0.5H), 4.06-3.95 (m, 0.5H), 3.67-3.34 (m, 4H), 3.24 (s, 3H).

Example 155

([±])-N-[1-methyl-3-(4'-chloro[1,1'-biphenyl]-4-yl)-3-oxopropyl]-N-hydroxyformamide

Example 155A

(E)-1-(4'-chloro[1,1'-biphenyl]-4-yl)but-2-en-1-one

A solution of 4-chlorodiphenyl (3.94g, 0.02mol) and crotonyl chloride (2 mL, 0.02 mol) in CH₂Cl₂ (50 mL) was treated with AlCl₃ (2.78 g, 0.02 mol) at rt, stirred overnight, quenched with H₂O, extracted with CH₂Cl₂, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification on silica gel with 5% CH₂Cl₂/hexanes provided 2.6 g (51%) of the desired compound.

Example 155B

([±])-3-(hydroxyamino)-1-(4'-chloro[1,1'-biphenyl]-4-yl)-1-butanone

A solution of Example 155A (0.1 g, 0.39 mmol), N H₂OH•HCl (0.13 g, 1.95 mmol), and K₂CO₃ (0.27 g, 1.95 mmol) in THF (50 mL) was refluxed for 5h, quenched with H₂O, extracted with ethyl acetate, dried over MgSO₄, filtered, and concentrated. Purification on silica gel with 1% methanol/CH₂Cl₂ provided 0.009 g (8%) of the desired compound.

Example 155C

([±])-N-[1-methyl-3-(4'-chloro[1,1'-biphenyl]-4-yl)-3-oxopropyl]-N-hydroxyformamide

Example 155C was formylated according to the procedure of Example 1E to give the title compound.

MS (ESI) 318 (M+H), 335 (M+NH₄), 340 (M+Cl), 316 (M-H);

¹H NMR (300MHz, DMSO-d₆-) δ 9.80 (s, 0.5H), 9.32 (s, 0.5H), 8.20 (s, 0.5H), 8.04 (d, 2H, J=8.2 Hz), 7.82 (dd, 4H, J=14.9, 8.4 Hz), 7.57 (d, 2H, J=8.5 Hz), 4.91-4.79 (m, 0.5H),

4.50-4.36 (m, 0.5H), 3.54 (dd, 1H, J=17.6, 8.1 Hz), 3.10 (dd, 1H, J=17.0, 4.1 Hz), 1.26 (d, 1.5H, J=6.7 Hz), 1.18 (d, 1.5H, J=6.5 Hz);

Anal. calcd for C₁₇H₁₆NO₃Cl·0.25 H₂O: C, 63.35; H, 5.16; N, 4.34. Found: C, 63.01; H, 5.42; N, 4.08.

5

Example 156

([±])-N-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-(4-butylphenoxy)-phenyl]sulfonyl]ethyl]-N-hydroxyformamide

10

The title compound was prepared according to the procedures of Example 61, except substituting 4-(4'-n-butylphenoxy)benzenethiol in place of 4'-thiol-4-biphenyl-carbonitrile in Example 61A.

MS (ESI) 532 (M+H), 549 (M+NH₄), 554 (M+Na), 530 (M-H);

15

¹H NMR (300MHz, DMSO-d₆) δ 9.69 (s, 0.5H), 9.52 (s, 0.5H), 8.09 (s, 0.5H), 7.87 (dd, 2H, J=8.8, 3.0 Hz), 7.68 (s, 0.5H), 7.28 (d, 2H, J=8.5 Hz), 7.14-7.04 (m, 4H), 4.90-4.78 (m, 0.5H), 4.51-4.40 (m, 0.5H), 3.74-3.40 (m, 4H), 2.76 (s, 0.5H), 2.76 (s, 1.5H), 2.61 (t, 2H, J=7.5 Hz), 1.63-1.52 (m, 2H), 1.39-1.26 (m, 2H), 1.26-1.22 (m, 6H), 0.91 (t, 3H, J=7.2 Hz);

20

Anal. calcd for C₂₆H₃₃N₃O₇S: C, 58.74; H, 6.25; N, 7.90. Found: C, 58.50; H, 6.43; N, 7.76.

Example 157

([±])-N-[3-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)-1-[[4-(4-(trifluoromethyl)phenoxy)phenyl]sulfonyl]methyl]propyl]-N-hydroxyformamide

25

The title compound was prepared according to the procedures of Example 61, except substituting 4-(4'-trifluoromethylphenoxy)-benzenethiol in place of 4'-thiol-4-biphenylcarbonitrile and Example 47A in place of Example 16B.

MS (ESI) 544 (M+H), 566 (M+Na), 542 (M-H);

30

¹H NMR (300MHz, DMSO-d₆) δ 9.97 (s, 0.5H), 9.60 (s, 0.5H), 8.32 (s, 0.5H), 8.23 (s, 0.5H), 8.11 (s, 0.5H), 7.95-7.89 (m, 2H), 7.82 (d, 2H, J=8.8 Hz), 7.76 (s, 0.5H), 7.35-7.28 (m, 4H), 4.54-4.42 (m, 0.5H), 4.06-3.95 (m, 0.5H), 3.68-3.22 (m, 4H), 2.04-1.62 (m, 2H), 1.26 (s, 3H), 1.23 (s, 3H).

Example 158

(\pm)-N-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-(4-(trifluoromethoxy)phenoxy)phenyl]sulfonyl]ethyl]-N-hydroxyformamide

5

The title compound was prepared according to the procedures of Example 61, except substituting 4-(4'-trifluoromethoxyphenoxy)-benzenethiol in place of 4'-thiol-4-biphenylcarbonitrile and Example 26A in place of Example 16b.

10 MS (ESI) 546 (M+H), 568 (M+Na), 544 (M-H);

^1H NMR (300MHz, DMSO- d_6) δ 9.64 (s, 0.5H), 9.45 (s, 0.5H), 8.35 (d, 1H, J=12.2 Hz), 8.10 (s, 0.5H), 7.91 (dd, 2H, J=8.9, 2.8 Hz), 7.68 (s, 0.5H), 7.47 (d, 2H, J=9.2 Hz), 7.30-7.21 (m, 4H), 4.88-4.77 (m, 0.5H), 4.51-4.40 (m, 0.5H), 3.73-3.38 (m, 4H), 1.24 (s, 3H), 1.22 (s, 3H);

15 Anal. calcd for $\text{C}_{22}\text{H}_{22}\text{N}_3\text{O}_8\text{SF}_3$: C, 48.44; H, 4.06; N, 7.70. Found: C, 48.34; H, 4.29; N, 7.54.

Example 159

(\pm)-N-[1-[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-3-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]propyl]-N-hydroxyformamide

20

The title compound was prepared according to the procedures of Example 61, except substituting 4-(4'-chlorophenoxy)-benzenethiol in place of 4'-thiol-4-biphenylcarbonitrile and 1-bromo-4-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)butan-2-one in place of Example 16b.

25

MS (ESI) 524 (M+H), 541 (M+NH₄), 546 (M+Na), 522 (M-H);

^1H NMR (300MHz, DMSO- d_6) δ 9.97 (s, 0.5H), 9.60 (s, 0.5H), 8.10 (s, 0.5H), 7.89-7.84 (m, 2H), 7.76 (s, 0.5H), 7.53 (d, 2H, J=8.9 Hz), 7.25-7.16 (m, 4H), 4.50-4.38 (m, 0.5H), 4.04-3.92 (m, 0.5H), 3.64-3.24 (m, 4H), 2.79 (s, 1.5H), 2.75 (s, 1.5H), 2.02-1.86 (m, 1H), 1.74-1.61 (m, 1H), 1.27 (s, 3H), 1.24 (s, 3H);

30

Anal. calcd for $\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_7\text{SCl} \cdot 0.5 \text{H}_2\text{O}$: C, 51.83; H, 5.10; N, 7.88. Found: C, 51.84; H, 4.95; N, 7.92.

Example 160

([±])-N-[2-[4-(4'-cyano[1,1'-biphenyl]-4-yl)oxy]cyclohexyl]-N-hydroxyformamide

The title compound was prepared from 2-chlorocyclohexanone first by alkylating with 4'-hydroxy-4-biphenylcarbonitrile as described in Example 16C, then converting the resulting ketone to the title compound through the oxime formation, reduction and formylation procedures described in examples 2D, 2E and 2F.

MS(ESI): 337(M+H), 354(M+18), 359(M+23), 673(2M+H), 695(2M+23);

¹H NMR (300MHz, DMSO-d₆): δ 9.90(s, 0.2 H), 9.69(s, 0.3H), 9.48(s, 0.5H), 8.27(s, 0.2H), 8.05 (s, 0.3H), 8.01(s, 0.5H), 7.93-7.78(m, 4H), 7.67(m, 2H), 7.06(m, 2H), 4.55-4.17(m, 1H), 3.80-3.68(m, 1H), 2.30-2.00(m, 1H), 1.88-1.22(m, 7H).

Example 161

([±])-N-[2-[4-[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]cyclohexyl]-N-hydroxyformamide

Example 161A

To a solution of 100 mg (0.434mmol) of (1S*, 2S*)-2-((*tert*-butyldimethylsilyl)oxy)-cyclohexanol, 132mg (0.521 mmol) of 4-(p-trifluoromethoxyphenyl)phenol and 342 mg (1.302mmol) of triphenylphosphine in 5ml THF under nitrogen at room temperature was added 171ml (1.085mmol) diethyl azodicarboxylate (DEAD). The resulting mixture was stirred at room temperature for 18h and then under reflux for 2 days. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with hexanes/ethyl acetate (24:1) to give 55 mg (27%) of the title compound as colorless oil.

MS(ESI): 467(M+H), 484 (M+NH₄).

Example 161B

([±])-N-[2-[4-[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]cyclohexyl]-N-hydroxyformamide

The title compound was prepared from Example 161A, by first deprotecting the silyl ether as in Example 4D, then applying the sequence of reactions described in Examples 1C, 1D and 1E.

MS(ESI): 396 (M+H), 413 (M+18), 418 (M+23), 813 (2M+23);

¹H NMR (CD₃OD): δ 8.29 (s, 0.3H), 8.05 (s, 0.7H), 7.63 (d, J=7.5Hz, 2H), 7.52 (d, J=7.5 Hz, 2H), 7.29 (d, J=7.5 Hz, 2H), 7.02 (d, J=7.5 Hz, 2H), 4.55-4.30 (m, 1.3H), 3.72 (m, 0.7H), 2.38-2.28 (m, 1H), 2.00-1.72 (m, 3H), 1.52-1.20 (m, 4H).

Example 162

([±])-1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(3-methyl-6-oxo-1(6H)-pyridazinyl)ethyl]-N-hydroxyformamide

Example 162A

([±])-1-[3-[4-(4-chlorophenoxy)phenyl]thio]-2-hydroxypropyl]-3-methyl-1H-pyridazin-6-one

The title compound was prepared following the procedures of Example 1A and 1B, except substituting 6-methyl-3-[2H]-pyridazinone for phenol in Example 1A and 4-(4'-chlorophenoxy)benzene thiol for 4'-hydroxy-4-biphenylcarbonitrile in Example 1B.

Example 162B

([±])-1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(3-methyl-6-oxo-1(6H)-pyridazinyl)ethyl]-N-hydroxyformamide

Example 162A was converted to the title compound following the procedures described in Examples 2C-2F (inclusive) and 46D.

MS (ESI) m/z 478 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 9.79 (br, 0.5H), 9.52 (br, 0.5H); 8.04 (s, 0.5H), 7.89-7.84 (m, 2H), 7.66 (s, 0.5H), 7.55-7.52 (m, 2H), 7.32 (d, 1H), 7.23-7.16 (m, 4H), 6.86 (d, 1H), 5.04-4.95 (m, 0.5H), 4.58-4.49 (m, 0.5H), 4.26-4.18 (m, 1H), 4.12-4.05 (m, 1H), 3.79-3.66 (m, 1H), 3.56-3.51 (m, 1H), 2.22-2.20 (m, 3H);

Anal. calcd for C₂₁H₂₀ClN₃O₆S: C, 52.78; H, 4.22; N, 8.79. Found: C, 52.71; H, 4.45; N, 8.49.

Example 163

(⁺)-N-hydroxy]-[1-[(6-oxo-1(6H)-pyridazinyl)methyl]-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy]ethyl]formamide

The title compound was prepared following the procedures of Example 134 except substituting 3-[2H]-pyridazinone for 5,5-dimethylloxazolidin-2,4-dione.

MS (ESI) m/z 450 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 9.97 (br, 0.5H), 9.61 (br, 0.5 H), 8.28 (s, 0.5H), 7.96-7.92 (m, 1H), 7.87 (s, 0.5H), 7.76-7.72 (m, 2H), 7.65-7.61 (m, 2H), 7.46-7.40 (m, 3H), 7.04-6.94 (m, 3H), 5.09-5.00 (m, 0.5H), 4.59-4.50 (m, 0.5H), 4.46-4.11 (m, 4H);

Anal. calcd for C₂₁H₁₈F₃N₃O₆: C, 56.13; H, 4.04; N, 9.35. Found: C, 56.23; H, 3.79; N, 9.36.

Example 164

(⁺)-N-[1-[(1,6-dihydro-3-methyl-2,6-dioxo-1(6H)-pyrimidinyl)methyl]-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures of Example 162 except substituting 1-methyluracil for 6-methyl-3-[2H]-pyridazinone and 4-(4'-trifluoromethoxy-phenoxy)benzene thiol for 4-(4'-chlorophenoxy)benzene thiol.

MS (ESI) m/z 544 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 9.52 (br, 0.5H), 9.42 (br, 0.5H), 8.04 (s, 0.5H), 7.89-7.85 (m, 2H), 7.73 (s, 0.5H), 7.70-7.66 (m, 1H), 7.49-7.46 (m, 2H), 7.31-7.26 (m, 2H), 7.22-7.18 (m, 2H), 5.64 (d, 1H), 4.99-4.90 (m, 0.5H), 4.43-4.34 (m, 0.5H), 4.03-3.87 (m, 2H), 3.75-3.63 (m, 1H), 3.52-3.41 (m, 1H), 3.17 (s, 3H);

Anal. calcd for C₂₂H₂₀F₃N₃O₈S: C, 48.62; H, 3.71; N, 7.73. Found: C, 48.84; H, 3.99; N, 7.55.

Example 165

(⁺)-N-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-(4-bromophenoxy)phenyl)sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures of Example 61, except substituting 4-(4'-bromophenoxy)benzene thiol in place of 4'-thiol-4-biphenylcarbonitrile.

MS (ESI) m/z 573 ($M+H$)⁺;

¹H NMR (300 MHz, DMSO- d_6) δ 9.70 (br, 0.5H), 9.51 (br, 0.5H), 8.09 (s, 0.5H), 7.91-7.88 (m, 2H), 7.68 (s, 0.5H), 7.66-7.62 (m, 2H), 7.22-7.19 (m, 2H), 7.16-7.12 (m, 2H), 4.88 (m, 0.5H), 4.49-4.42 (m, 0.5H), 3.71-3.42 (m, 4H), 2.77 (s, 1.5H), 2.76 (s, 1.5H), 1.25-1.23 (m, 6H);

Anal. calcd for $C_{22}H_{24}BrN_3O_7S$: C, 47.66; H, 4.36; N, 7.58. Found: C, 48.21; H, 4.79; N, 7.23.

Example 166

([±])-*N*-[1-[(2,5-dioxo-4,4-dimethyl-1-imidazolidinyl)methyl]-2-methyl-2-[[4'-(trifluoromethoxy)][1,1'-biphenyl]-4-yl]oxy]propyl]-*N*-hydroxyformamide

Example 166A

3-bromo-3-methyl-2-butanone

A solution of 3-methyl-2-butanone (5 mL, 4.67 mol) in 70 mL of THF at 0 °C was treated with phenyltrimethylammonium tribromide, stirred 30 min at 0 °C, quenched with $NaHCO_3$, filtered, and concentrated to provide 7.5 g (97%) of the title compound.

¹H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 1.87 (s, 6H).

Example 166B

3-methyl-3-[[4'-(trifluoromethoxy)][1,1'-biphenyl]-4-yl]oxy]-2-butanone

A soln of 4-(4-trifluoromethoxyphenyl)phenol (6 g, 23.6 mmol) in 23 mL of DMF was treated with potassium carbonate (4 g) and Example 166A (5 g), stirred at rt for 16 h, filtered, and concentrated to provide 4.4 g (55%) of the title compound.

MS (ESI) m/z 356 ($M+18$)⁺.

Example 166C

1-bromo-3-methyl-3-[[4'-(trifluoromethoxy)][1,1'-biphenyl]-4-yl]oxy]-2-butanone

A soln of Example 166B (4.4 g, 13.2 mmol) in 40 mL of CHCl₃ at 0 °C was treated with bromine (1 mL), stirred at rt for 30 min, quenched with 2:1 satd NaHCO₃/10% NaHSO₃, extracted with ethyl acetate (2 x 50 mL), washed with brine, dried over Na₂SO₄, filtered, and concentrated to provide 5.5 g (100%) of the title compound.

MS (ESI) m/z (M+18)⁺.

Example 166D

([±])-1-[(2,5-dioxo-4,4-dimethyl-1-imidazolidinyl)-3-methyl-3-[4'-(trifluoromethoxy)]1,1'-biphenyl]-4-yl]oxy]-2-butanone

A soln of Example 166C (5.5 g, 13.2 mmol) in 26 mL of DMF was treated with 5,5-dimethylhydantoin (1.69 g) and potassium carbonate (1.82 g), stirred at rt for 16 h, diluted with 150 mL of CHCl₃, filtered, and concentrated. Purification on silica gel with 1:1 hexanes/ethyl acetate provided 4.05 g (66%) of the title compound.

MS (ESI) m/z 463 (M-1)⁻.

Example 166E

([±])-N-[1-[(2,5-dioxo-4,4-dimethyl-1-imidazolidinyl)-2-methyl-2-[4'-(trifluoromethoxy)]1,1'-biphenyl]-4-yl]oxy]hydroxylamine

A soln of Example 166D (550 mg, 1.18 mmol) in 6 mL of 1:1 THF/ethanol was treated with hydroxylamine•HCl (99 mg) and pyridine (115 µL), heated at 75-80 °C for 8 h, cooled to 0 °C, treated with borane•pyridine (359 µL) and HCl (1.78 mL, 4N in dioxane), stirred 16 h at rt, quenched with satd NaHCO₃, extracted with ethyl acetate (3 x 20 mL), washed with brine, dried over Na₂SO₄, filtered, and concentrated. Purification on silica gel with 1:2 hexanes/ethyl acetate provided 230 mg (40%) of the title compound.

MS (ESI) m/z 482 (M+H)⁺.

Example 166F

([±])-N-[1-[(2,5-dioxo-4,4-dimethyl-1-imidazolidinyl)methyl]-2-methyl-2-[4'-(trifluoromethoxy)]1,1'-biphenyl]-4-yl]oxy]propyl]-N-hydroxyformamide

Example 166E was converted to the title compound following the formylation procedure described in Example 1E.

MS (ESI) m/z 510 ($M+1$)⁺;

- ¹H NMR (300 MHz, DMSO- d_6) δ 9.56 (br, 0.5H), 9.39 (br, 0.5H), 8.40 (br, 0.5H), 8.38 (br, 1H), 8.32 (s, 0.5H), 7.94 (s, 0.5H), 7.80-7.76 (m, 2H), 7.65-7.60 (m, 2H), 7.45-7.42 (m, 2H), 7.24-7.16 (m, 2H), 4.70 (dd, 0.5H), 4.26 (dd, 0.5H), 4.12-3.98 (m, 1H), 3.91-3.79 (m, 1H), 1.38-1.25 (m, 12H).

Example 167

- 10 (⁺)-*N*-[1-[[4-[(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(1,6-dihydro-3-methyl-2,6-dioxo-1(6H)-pyrimidinyl)ethyl]-*N*-hydroxyformamide

The title compound was prepared following the procedures of Example 162 except substituting 1-methyluracil for 6-methyl-3-[2H]-pyridazinone.

- 15 MS (ESI) m/z 511 ($M+18$)⁺;

¹H NMR (300 MHz, DMSO- d_6) δ 9.52 (br, 0.5H), 9.43 (br, 0.5H), 8.04 (s, 0.5H), 7.87-7.83 (m, 2H), 7.73 (s, 0.5H), 7.70 (d, 0.5H), 7.66 (d, 0.5H), 7.55-7.50 (m, 2H), 7.22-7.15 (m, 4H), 5.64 (d, 1H), 4.99-4.90 (m, 0.5H), 4.42-4.34 (m, 0.5H), 4.04-3.86 (m, 2H), 3.74-3.62 (m, 1H), 3.52-3.40 (m, 1H), 3.26 (s, 3H);

- 20 Anal. calcd for C₂₁H₂₀ClN₃O₇S: C, 51.07; H, 4.08; N, 8.51. Found: C, 51.35; H, 4.29; N, 8.40.

Example 168

- 25 (⁺)-*N*-hydroxy-*N*-[1-[(3-methyl-6-oxo-1(6H)-pyridazinyl)methyl]-2-[[4-(4-(trifluoromethoxy)phenoxy)phenyl]sulfonyl]ethyl]formamide

The title compound was prepared following the procedures of Example 162 except substituting 4-(4'-trifluoromethoxyphenoxy)benzene thiol for 4-(4'-chlorophenoxy)benzene thiol.

- 30 MS (ESI) m/z 528 ($M+H$)⁺;

¹H NMR (300 MHz, DMSO- d_6) δ 9.78 (br, 0.5H), 9.50 (br, 0.5H), 8.03 (s, 0.5H), 7.91-7.86 (m, 2H), 7.65 (s, 0.5H), 7.49 (d, 2H), 7.34-7.26 (m, 3H), 7.22-7.18 (m, 2H), 6.86 (d,

1H), 5.06 (m, 0.5H), 4.60-4.48 (m, 0.5H), 4.27-4.18 (m, 1H), 4.13-4.06 (m, 1H), 3.80-3.66 (m, 1H), 3.59-3.49 (m, 1H), 2.22 (d, 3H);

Anal. calcd for C₂₂H₂₀F₃N₃O₇S: C, 50.10; H, 3.82; N, 7.97. Found: C, 50.21; H, 3.97; N, 7.96.

5

Example 169

([±])-N-hydroxy-N-[1-(1-methyl-1H-indol-4-yl)-[2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

10 The title compound was prepared according to the procedures of Example 126, except substituting methyl 1-methyl-4-indolecarboxylate for ethyl methoxyacetate and 4-(4'-trifluoromethoxyphenyl)-phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)-phenyl methyl sulfone.

MS (ESI) 533 (M-H);

15 ¹H NMR (300 MHz, DMSO-d₆) δ 9.95 (s, 0.5H), 9.56 (s, 0.5H), 8.13 (s, 0.5H), 7.90-7.85 (d, 2H, J=8.9 Hz), 7.50-7.40 (m, 4H), 7.2-7.0 (m, 6H), 6.53 (s, 1H), 6.1 (s, 0.5H), 5.70 (s, 0.5H), 4.15 (m, 2H), 3.7-3.65 (m, 4H);

Anal. calcd for C₂₅H₂₁N₂O₆SF₃: C, 56.17; H, 3.96; N, 5.24. Found: C, 56.33; H, 4.38; N, 4.78.

20

Example 170

([±])-N-hydroxy-N-[1-(1-methyl-1H-indol-2-yl)-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

25 The title compound was prepared according to the procedures of Example 126, except substituting methyl 1-methyl-2-indolecarboxylate for ethyl methoxyacetate and 4-(4'-trifluoromethoxyphenyl) phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)-phenyl methyl sulfone.

MS (ESI) 533 (M-H);

30 ¹H NMR (300 MHz, DMSO-d₆) δ 9.9 (s, 0.5H), 9.6 (s, 0.5H), 7.9-7.85 (d, 2H, J=8.8 Hz), 7.52-7.48 (d, 2H, J=8.8 Hz), 7.4-7.35 (m, 2H), 7.25-7.20 (d, 2H, J=8.67 Hz), 7.15-7.00 (m, 4H), 6.40 (s, 0.5H), 6.1 (s, 0.5H), 4.2 (s, 1H), 4.05-3.90 (m, 2H), 3.75 (s, 3H);

Anal. calcd for C₂₅H₂₁N₂O₆SF₃ 0.25 ethyl acetate: C, 56.11; H, 4.16; N, 5.03. Found: C, 56.62; H, 4.49; N, 4.80.

Example 171

5 (⁺)-N-[1-(4-chlorophenyl)-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of Example 75, except substituting 4-chlorobenzaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenyl)phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in Example 75A.

MS (ESI) 548 (M-H);

¹H NMR (300 MHz, DMSO-d₆) δ 10.25 (s, 0.5H), 9.70 (s, 0.5H), 8.25-8.1 (m, 1H), 7.90-7.85 (d, 2H, J=8.6 Hz), 7.77-7.70 (d, 2H, J=8.8 Hz), 7.65 (s, 1H), 7.52-7.46 (d, 2H, J=8.7 Hz), 7.23-7.10 (d, 2H, J=8 Hz), 5.87 (s, 0.5H), 5.55 (s, 0.5H), 4.20-4.00 (m, 3H);

Anal. calcd for C₂₃H₁₇NO₆SF₆ 1.25 ethyl acetate: C, 48.29; H, 3.43; N, 2.44. Found: C, 48.01; H, 3.00; N, 2.00.

Example 172

20 (⁺)-N-hydroxy-N-[2-[[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-1-[4-(trifluoromethyl)phenyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 75, except substituting 4-trifluoromethylbenzaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenyl)phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in Example 75A.

MS (ESI) 514 (M-H), 516 (M+H);

¹H NMR (300 MHz, DMSO-d₆) δ 10.01 (s, 0.5H), 9.65 (s, 0.5H), 8.25-8.15 (m, 1H), 7.90-7.80 (d, 2H, J=8.9 Hz), 7.55-7.49 (d, 8.7H), 7.4 (m, 3H), 7.34-7.25 (m, 3H), 7.20-7.15 (d, 2H, J=8.9 Hz), 5.7 (s, 0.5H), 5/48 (s, 0.5H), 4.25-4.0 (m, 3H);

Anal. calcd for C₂₂H₁₇NO₆SF₃Cl: C, 51.22; H, 3.32; N, 2.71. Found: C, 51.30; H, 3.35; N, 2.53.

Example 173

(⁺)-N-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures of Example 162, except using hydantoin on place of 6-methyl-3-[2H]-pyridazinone and 4-(4'-trifluoromethoxy-phenyl)benzenethiol in place of 4-(4'-chlorophenyl)benzenethiol.

MS (ESI) 518 (M+H), 535 (M+NH₄), 540 (M+Na), 516 (M-H);

¹H NMR (300 MHz, DMSO-d₆) δ 9.79 (s, 0.5H), 9.53 (s, 0.5H), 8.15 (d, 1H, J=6.6 Hz), 8.10 (s, 0.5H), 7.93-7.88 (m, 2H), 7.73 (s, 0.5H), 7.48 (d, 2H, J=9.2 Hz), 7.32-7.20 (m, 4H), 4.88-4.77 (m, 0.5H), 4.48-4.34 (m, 0.5H), 3.94-3.40 (m, 6H).

Example 174

(⁺)-N-hydroxy-N-[1-[(2-thienylthio)methyl]-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

Example 174A

methyl 2-(2-thienylthio)acetate

To a solution of thiophene-2-thiol (1.2 g, 10.3 mmol) in anhydrous DMF (30 mL) was added cesium carbonate (3.9 g, 12 mmol) and the resulting suspension was stirred for 15 min at ambient temperature, then treated with methyl bromoacetate (1.53 g, 10 mmol). The purple suspension was stirred for 1 h, then poured into water (30 mL) and extracted twice with 300 mL EtOAc. The combined organic extracts were washed with brine, dried, filtered, concentrated and the residue was purified via column chromatography eluting with 10% EtOAc/Hexanes to give 1.48 g (79%) of the title compound.

Example 174B

(⁺)-N-hydroxy-N-[1-[(2-thienylthio)methyl]-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 126, except substituting Example 174A for ethyl methoxyacetate and 4-(4'-trifluoromethoxy-phenoxy)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

mp 120-122 °C;

MS (ESI(+)) 533 (M+NH₄-H₂O), 550 (M+NH₄), 555 (M+Na);

¹H NMR (300 MHz, DMSO-d₆): δ 10.12 (bs, 1/2H), 9.80 (bs, 1/2H), 8.35 (s, 1/2H), 7.89-7.98 (m, 2.5H), 7.73-7.79 (m, 1H), 7.55-7.63 (m, 2H), 7.34-7.42 (m, 2H), 7.23-7.32 (m, 3H), 7.11-7.20 (m, 1H), 4.72-4.82 (m, 1/2H), 4.04-4.13 (m, 1/2H), 3.63-3.88 (m, 2H), 2.99-3.19 (m, 2H);

Anal. calcd for C₂₁H₁₈F₃NO₆S₃: C, 47.27; H, 3.40; N, 2.62; S, 18.02, F, 10.68. Found: C, 47.05; H, 3.43; N, 2.82; S, 17.83, F, 10.37 .

Example 175

([±])-N-hydroxy-N-[1-[[[(4-methylphenyl)sulfonyl]methylamino]methyl]-2-[[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

Example 175A

ethyl 2-[methyl[(4-methylphenyl)sulfonyl]amino]acetate

An ice cold suspension of sarcosine ethyl ester hydrochloride salt (3.1 g, 20 mmol) in CH₂Cl₂ (150 mL) was sequentially treated with triethyl amine (4.45 g, 44 mmol) and tosyl chloride (4.19 g, 22 mmol) and stirred for 1h, after which time the ice bath was removed, and the reaction was allowed to stir for an additional 1h. The reaction mixture was then partitioned between water and CH₂Cl₂ and the organic extract was washed with brine, dried, filtered, and concentrated to give 5.7 g of the title compound as a white solid.

Example 175B

([±])-N-hydroxy-N-[1-[[[(4-methylphenyl)sulfonyl]methylamino]methyl]-2-[[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 126, except substituting Example 175A for ethyl methoxyacetate and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone. mp 160.7-162.5 °C;

¹H NMR (300 MHz, DMSO-d₆): δ 9.97 (bs, 1/2H), 9.72 (bs, 1/2H), 8.18 (s, 1/2H), 7.88-7.98 (m, 2H), 7.82 (s, 1/2H), 7.59-7.68 (m, 2H), 7.37-7.50 (m, 4H), 7.20-7.32 (m, 4H),

4.76-4.85 (m, 1/2H), 4.25-4.36 (m, 1/2H), 3.62 (dd, 1H, J=14, 8 Hz), 3.44-3.56 (m, 1H), 3.25 (dd, 1/2H, J=8, 14 Hz), 3.07 (d, 1/2H, J=8 Hz), 2.90 (dd, 1/2H, J=14, 8 Hz), 2.59-2.66 (m, 1.5H), 2.54-2.59 (m, 1H), 2.48-2.54 (m, 1H), 2.40 (s, 3H);
MS (ESI(-)) 600.8 (M-H), 636.9 (M+Cl), 1203.4 (2M-H);

- 5 Anal. calcd for $C_{25}H_{25}F_3N_2O_8S_2$: C, 49.82; H, 4.18; N, 4.65; S, 10.64; F, 9.46. Found: C, 49.67; H, 4.19; N, 4.50; S, 10.59; F, 9.38.

Example 176

- 10 (\pm) -N-hydroxy-N-[[2-(methoxyethoxy)methyl]-1-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 126, except substituting ethyl (2'-methoxy)ethoxyacetate for methyl methoxyacetate and 4-(4'-trifluoromethoxyphenyl)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

- 15 MS (ESI-) 492 (M-H);

1H NMR (DMSO- d_6) δ 3.22 (s, 3H), 3.42-3.66 (m, 8H), 4.14-4.25 (m, 0.5H), 4.68-4.79 (m, 0.5H), 7.23 (d, 2H, J=9 Hz), 7.28 (d, 2H, J=9 Hz), 7.48 (d, 2H, J=9 Hz), 7.83 (s, 0.5H), 7.93 (d, 2H, J=9 Hz), 8.14 (s, 0.5H), 9.55 (bs, 0.5H), 9.96 (bs, 0.5H);

- 20 Anal. calcd for $C_{20}H_{22}NO_8SF_3$: C, 48.68; H, 4.49; N, 2.83. Found: C, 48.61; H, 4.60; N, 2.80.

Example 177

- 25 (\pm) -N-[1-[(1,6-dihydro-3-methyl-2,6-dioxo-1(6H)-pyrimidinyl)methyl]-2-[[4-(phenoxyphenyl)sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures of Example 162, except using 4-(phenoxy)-benzenethiol in place of 4-(4'-chlorophenoxy)-benzenethiol.

MS (ESI) m/z 460 (M+H) $^+$;

- 30 1H NMR (300 MHz, DMSO- d_6) δ 9.55 (br, 0.5H), 9.47 (br, 0.5H), 8.05 (s, 0.5H), 7.86-7.83 (m, 2H), 7.74 (s, 0.5H), 7.71-7.67 (m, 2H), 7.52-7.47 (m, 2H), 7.30-7.25 (m, 2H), 7.19-7.11 (m, 4H), 5.64 (d, 1H), 4.99-4.91 (m, 0.5H), 4.42-4.34 (m, 0.5H), 4.05-3.85 (m, 2H), 3.73-3.62 (m, 1H), 3.51-3.39 (m, 1H), 3.27 (s, 3H);

Anal. calcd for C₂₁H₂₁N₃O₇S: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.01; H, 4.91; N, 8.90.

Example 178

5 ([±])-N-hydroxy-N-[1-(4-hydroxyphenyl)-2-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide

A suspension of Example 129 (186 mg, 0.366 mmol) in dichloromethane (20 mL) at -78 °C was treated with boranetrifluoride diethyl etherate (55.6 mL, 0.439 mmol), stirred at 0 °C for 3 hours and left at room temperature overnight, treated with water, extracted with ethyl acetate, dried (Na₂SO₄), filtered, concentrated and purified on silica gel with 80% ethyl acetate/hexanes to provide 45 mg (26%) of the title compound as an orange solid.

mp 225 °C decomposed;

15 MS (ESI) m/z 466 (M+H)⁺, 483 (M+NH₄), 464 (M-H)⁻, 488 (M+Na)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 3.90-4.22 (br, 2H), 5.32 (br, 0.5H), 5.66 (br, 0.5H), 6.61-6.64 (d, 2H, J=9 Hz), 7.00-7.20 (2H), 7.84-8.23 (m, 10H), 9.50 (s, 1H);

Anal. calcd for C₂₂H₁₈NF₃O₅S 0.25 H₂O: C, 56.22; H, 3.96; N, 2.98. Found: C, 56.09; H, 4.00; N, 2.83.

Example 179

([±])-N-hydroxy-N-[1-(2,2-dimethyl-1,3-dioxan-5-yl)-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

Example 179A

([±])-N-[1-(2,2-dimethyl-1,3-dioxan-5-yl)-2-[[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]hydroxylamine

The title compound was prepared according to the procedures of Example 126A, 126B, 75C except substituting 2,2-dimethyl-5-ethylcarboxylate-1,3-dioxane (*Tetrahedron*

1991, 47, 1001) for methyl methoxyacetate and 4-(4'-trifluoromethoxyphenyl)-phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)-phenyl methyl sulfone.

Example 179B

(⁺)-*N*-hydroxy-*N*-[1-(2,2-dimethyl-1,3-dioxan-5-yl)-2-[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

Example 179A was converted to the title compound following the fomylation procedure of Example 75D.

mp 139.5-140.7 °C;

MS (ESI) *m/z* 520 (M+H)⁺, 542 (M+Na)⁺, 518 (M-H)⁻, 554 (M+Cl)⁻;

¹H NMR (300 MHz, DMSO-*d*₆) δ 1.17-1.30 (6H), 3.36-3.77 (m, 5H), 3.79-3.92 (0.75H), 4.03 (0.25H), 4.15-4.24 (m, 0.75H), 6.57-4.68 (0.25H), 7.19-7.28 (m, 4H), 7.42-7.50 (d, 2H, *J*=9Hz), 7.76 (s, 0.75H), 7.88-7.96 (m, 2H), 8.12 (s, 0.25H), 9.71 (br, 0.75H);

Anal. calcd for C₂₂H₂₄NF₃O₈S: C, 50.86; H, 4.65; N, 2.69. Found: C, 50.99; H, 4.97; N, 2.73.

Example 180

(⁺)-*N*-hydroxy-*N*-[3-hydroxy-2-(hydroxymethyl)-1-[[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]methyl]propyl]formamide

Example 179A was converted to the title compound following the procedures of Example 141A and B.

mp 129.2-131.3 °C;

MS (ESI) *m/z* 480 (M+H)⁺, 502 (M+Na)⁺, 478 (M-H)⁻;

¹H NMR (300 MHz, DMSO-*d*₆) δ 1.69-1.79 (m, 1H), 3.57-3.80 (m, 2H), 3.24-3.51 (m, overlapped w/solventH), 4.13-4.19 (dt, 1H, *J*=1.5, 8.4 Hz), 4.64-4.70 (1H), 7.19-7.30 (m, 4H), 7.45-7.48 (d, 2H, *J*=9 Hz), 7.678 (s, 0.7H), 7.86-7.90 (m, 2H), 8.04 (s, 0.3H);

Anal. calcd for C₁₉H₂₀NF₃O₈S.0.25 H₂O: C, 47.15; H, 4.26; N, 2.89. Found: C, 47.29; H, 4.44; N, 2.56.

Example 181

(\pm)-N-hydroxy-N-[1-(hydroxymethyl)-2-[[[4-chlorophenyl]thio]phenyl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 125, except substituting *tert*-butyldimethylsilyloxy-acetaldehyde for 3-*tert*-butyldimethylsilyloxypropionaldehyde and 4-(4'-chlorophenylthio)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

mp 148.5-150.0 °C;

MS (ESI) *m/z* 402 (M+H)⁺, 424 (M+Na)⁺, 400 (M-H)⁻;

¹H NMR (300 MHz, DMSO-*d*₆) δ 3.30-3.62 (m, overlaped w/ solventH), 3.90-4.01 (m, 0.5H), 4.47-4.60 (m, 0.3H, J=1.5), 5.01 (br, 0.7H), 7.36-7.39 (d, 2H, J=9Hz), 7.73-7.85 (m, 2.7H), 8.11 (s, 0.3H), 9.41 (brs, 0.7H), 9.83 (brs, 0.3H);

Anal. calcd for C₁₆H₁₆NCIO₅S₂: C, 47.81; H, 4.01; N, 3.48. Found: C, 47.55; H, 4.14; N, 3.28.

Example 182

(\pm)-N-hydroxy-N-[1-(4-morpholinylmethyl)-2-[[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of Example 126, except substituting methyl morpholinoacetate for ethyl methoxyacetate and 4-(4'-trifluoromethoxyphenyl)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

mp 160.9-162.7 °C;

MS (ESI) *m/z* 505 (M+H)⁺, 527 (M+Na)⁺, 503 (M-H)⁻, 539(M+Cl)⁺;

¹H NMR (300 MHz, DMSO-*d*₆) δ 2.10-2.42 (m, 6H), 3.48-3.65 (m, 6H), 4.13 (br, 0.6H), 4.68 (br, 0.4H), 7.18-7.32 (m, 4H), 7.46-7.49 (d, 2H, J=9Hz), 7.84-7.95 (2.6H), 8.14 (s, 0.4H), 9.46 (s, 0.6H), 9.88 (s, 0.4H);

Anal. calcd for C₂₁H₂₃N₂F₃O₇S: C, 49.99; H, 4.59; N, 5.55. Found: C, 49.77; H, 4.62; N, 5.39.

Example 183

([±])-N-hydroxy-N-[4-hydroxy-1-[[[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]methyl]butyl]formamide

The title compound was prepared according to the procedures of Example 125, except substituting 4-*tert*-butyldimethylsilyloxy-butanaldehyde for 3-*tert*-butyldimethylsilyloxy-propionaldehyde and 4-(4'-trifluoromethoxyphenyl)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

mp 92.0-93.9 °C;

MS (ESI) m/z 464 (M+H)⁺, 486 (M+Na)⁺, 462 (M-H)⁻;

¹H NMR (300 MHz, DMSO-d₆) δ 1.13-1.40 (m, 2H), 1.40-1.68 (m, 2H), 3.22-3.47 (m, overlaped w/ solventH), 3.53-3.68 (m, 1H), 4.02-4.13 (m, 0.5H), 4.37-4.49 (m, 1H), 4.49-4.58 (m, 0.45H), 7.20-7.23 (d, 2H, J=9Hz), 7.25-7.32 (dd, 2H, J=3, 9Hz), 7.46-7.49 (d, 2H, J=9Hz), 7.81 (s, 0.6H), 7.88-7.91 (d, 2H, J=9Hz), 8.12 (s, 0.4H), 9.46 (s, 0.6H), 9.83 (s, 0.4H);

Anal. calcd for C₁₉H₂₀NF₃O₇S: C, 49.24; H, 4.35; N, 3.02. Found: C, 49.22; H, 4.49; N, 2.95.

Example 184

([±])-N-[1-[(1*H*-isoindole-1,3(2*H*)-dione)methyl]-2-[[4-(4-chlorophenoxy)phenyl]sulfonyl]ethyl]-N-hydroxyformamide

Example 184A

2-(3-bromo-2-oxopropyl)-1*H*-isoindole-1,3(2*H*)-dione

The title compound was prepared following the procedures of examples 16A and 16B, except substituting phthalimide for 1,5,5-trimethylhydantoin in example 16A.

Example 184B

([±])-N-[1-[(1*H*-isoindole-1,3(2*H*)-dione)methyl]-2-[[4-(4-chlorophenoxy)phenyl]sulfonyl]ethyl]-N-hydroxyformamide

Alkylation of example 184A with 4-(4'-chlorophenoxy)benzene thiol as described in example 61A followed by the synthetic transformations described in example 61B and 61C gave the title compound.

¹H NMR (300 MHz, d₆-DMSO) δ 9.96 (br, 0.5H), 9.67 (br, 0.5H), 8.06 (s, 0.5H), 7.91-7.84 (m, 6H), 7.75 (s, o=0.5H), 7.55-7.51 (m, 2H), 7.22-7.13 (m, 4H), 5.01-4.91 (m, 0.5H), 4.56-4.46 (m, 0.5H), 3.89-3.62 (m, 4H);

MS (ESI) m/e 532 (M+18)⁺;

- 5 Anal. calcd for C₂₄H₁₉ClN₂O₇S: C, 55.98; H, 3.72; N, 5.44. Found: C, 56.09; H, 3.71; N, 5.31.

Example 185

- 10 (⁺)-N-[1-[(2,5-dioxo-3,4,4-trimethyl-1-imidazolidinyl)methyl]-2-[[4-(4-cyanophenoxy)phenyl]sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 61,

- 15 except substituting 4-(4'-cyanophenoxy)-benzene thiol for 4-thiol-4-biphenylcarbonitrile.
¹H NMR (300 MHz, d₆-DMSO) δ 9.74 (br, 0.5H), 9.52 (br, 0.5H), 8.10 (s, 0.5H), 7.97-7.90 (m, 4H), 7.68 (s, 0.5H), 7.36-7.28 (m, 4H), 4.89-4.79 (m, 0.5H), 4.52-4.42 (m, 0.5H), 3.76-3.37 (m, 4H), 2.76 (s, 1.5H), 2.76 (s, 1.5H), 1.26-1.23 (m, 6H);
MS (ESI) m/e 501 (M+H)⁺;
20 Anal. calcd for C₂₃H₂₄N₄O₇S: C, 55.19; H, 4.83; N, 11.19. Found: C, 55.39; H, 5.19; N, 10.96.

Example 186

- 25 (⁺)-N-hydroxy-N-[1-(2-pyridinyl)-2-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of example 75, except substituting 2-pyridine carboxaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in example 75A.

- 30 m.p.116.4-117.6 °C;
¹H NMR (300 MHz, DMSO-d₆) δ 3.88-4.04 (m, 1H), 4.28-4.36 (dd, 1H, J=4.5, 15Hz), 5.50 (br, 0.5H), 5.84 (br, 0.5H), 7.12-7.44 (m, 6H), 7.44-7.50 (d, 2H, J=9Hz), 7.74-7.95 (2H), 8.18 (s, 0.5H), 8.25 (s, 0.5H), 8.47 (1H), 9.66 (s, 0.5H);
35 MS (ESI) m/e 483 (M+H)⁺, 505 (M+Na)⁺, 481 (M-H)⁻, 517 (M+Cl)⁻;

Anal. calcd for $C_{21}H_{17}N_2F_3O_6S$: C, 52.28; H, 3.55; N, 5.80. Found: C, 51.95; H, 3.24; N, 5.63.

Example 187

(\pm)-N-[1-[[[(4-chlorophenoxy)phenyl]sulfonyl]methyl]-4-hydroxybutyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 125, except substituting 4-*tert*-butyldimethylsilyloxy-butanaldehyde for 3-*tert*-butyldimethylsilyloxypropionaldehyde and 4-(4'-chloro-phenoxy)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone

m.p. 126.9-128.8 °C;
1H NMR (300 MHz, DMSO- d_6) δ 1.20-1.38 (m, 2H), 1.41-1.65 (m, 2H), 3.35-3.44 (dd, 1H, J=3, 12 Hz), 3.52-3.67 (m, 1H), 4.01-4.13 (br, 0.4H), 4.33-4.58 (0.6H), 7.15-7.23 (dd, 4H, J=3, 9 Hz), 7.48-7.56 (d, 2H, J=9Hz), 7.81 (s, 0.6H), 7.85-7.92 (d, 2H, J=9Hz), 8.12 (s, 0.4H), 9.44 (br, 0.6H), 9.82 (br, 0.4H);
MS (ESI) m/e 414 (M+H) $^+$, 431 (M+NH $_4$) $^+$, 436 (M+Na) $^+$, 412 (M-H) $^-$;
Anal. calcd for $C_{18}H_{20}NClO_6S$: C, 52.23; H, 4.87; N, 3.38. Found: C, 52.21; H, 4.93; N, 3.21.

Example 188

(\pm)-N-[1-[[[(4-trifluoromethoxyphenoxy)phenyl]sulfonyl]methyl]-3-hydroxypropyl]-N-hydroxyformamide

The title compound was prepared according to the procedures of example 125, except substituting 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

m.p. 119.5-122.6 °C;
1H NMR (300 MHz, DMSO- d_6) δ 1.52-1.80 (m, 2H), 3.18-3.31 (m, 1H), 3.47-3.50 (1H), 3.54-3.72 (m, 1H), 4.20-4.32 (m, 0.7H), 4.43-4.49 (t, 0.3H, J=6Hz), 4.55-4.61 (t, 0.7H, J=6Hz), 4.64-4.76 (m, 0.3H), 7.17-7.26 (d, 2H, J= 9 Hz), 7.26-7.32 (2H), 7.43-7.51 (d, 2H, J=9Hz), 7.74 (s, 0.7H), 7.86-7.93 (d, 2H, J=9Hz), 8.09 (s, 0.3H), 9.46 (s, 0.7H), 9.81 (s, 0.3H);
MS (ESI) m/e 450 (M+H) $^+$, 467 (M+NH $_4$) $^+$, 472 (M+Na) $^+$, 448 (M-H) $^-$;

Anal. calcd for C₁₈H₁₈NF₃O₇S: C, 48.10; H, 4.03; N, 3.11. Found: C, 48.47; H, 4.10; N, 2.97.

Example 189

(⁺)-N-hydroxy-N-[1-[(4-trifluoromethoxyphenoxy)methyl]-2-[[4-(4-trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of example 126, except substituting ethyl 4-trifluoromethoxyphenoxy-acetate (prepared from ethyl bromoacetate and 4-trifluoromethoxy phenol as in example 174A) for ethyl methoxyacetate and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-trifluoromethylphenyl)phenyl methyl sulfone.

¹H NMR (DMSO-d₆) δ 3.55-3.79 (m, 2H), 3.96-4.15 (m, 2H), 4.38-4.50 (m, 0.5H), 4.86-4.97 (m, 0.5H), 6.95 (dd, 2H, J=3,9 Hz), 7.23 (d, 2H, J=9 Hz), 7.24-7.35 (m, 4H), 7.47 (d, 2H, J=9 Hz), 7.93 (d, 2H, J=6 Hz), 7.96 (s, 0.5H), 8.18 (s, 0.5H), 9.68 (bs, 0.5H), 10.08 (bs, 0.5H);

MS (ESI-) 594 (M-H);

Anal. Calcd for: C₂₄H₁₉NO₈SF₆ C, 48.40; H, 3.21; N, 2.35. Found: C, 48.35; H, 3.42; N, 2.35.

Example 190

[S-(R*,R*)]-N-hydroxy-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[4-[(4-phenyl-1-piperidiny)]phenyl]sulfonyl]ethyl]formamide

The title compound was prepared following the procedures described in example 145 starting with [4-(4-phenylpiperidine)phenyl]methyl sulfone (prepared by addition of 4-phenylpiperidine to (4-fluorophenyl)methyl sulfone) and commercially available methyl (R)-2,2-dimethyl-1,3-dioxolane-4-carboxylate.

¹H NMR (300 MHz, DMSO-d₆) δ 1.15-1.35 (m, 6H), 1.6-1.9 (m, 4H), 2.7-3.3 (m, 4H), 3.5-3.6 (m, 2H), 3.9-4.2 (m, 4.5H), 4.5-4.6 (t, 0.5H, J=5.6 Hz), 7.12 (d, 2H, J=9.3 Hz), 7.15-7.35 (m, 5H), 7.6-7.7 (m, 2H), 7.82 (s, 0.5H), 8.18 (s, 0.5H), 9.65 (s, 0.5H), 10.00 (br s, 0.5H);

MS (ESI+) 489 (M+H);

Anal. Calcd for C₂₅H₃₂N₂O₆S: C, 61.45; H, 6.60; N, 5.73. Found: C, 61.54; H, 6.53; N, 5.57.

Example 191

(⁺)-N-hydroxy-N-[1-(4-trifluoromethoxyphenyl)-2-[[4-(4-trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of example 75, except substituting 4-trifluoromethoxybenzaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in example 75A.

¹H NMR (300 MHz, DMSO-d₆) δ 4.0-4.2 (m, 4H), 5.45-5.55 (br m, 0.5H), 5.7-5.8 (br m, 0.5H), 7.14 (d, 2H, J=8.1 Hz), 7.20-7.35 (m, 4H), 7.35-7.60 (m, 4H), 7.84 (d, 2H, J=7.5 Hz), 8.1-8.3 (m, 1H), 9.66 (br s, 0.5H), 10.10 (br s, 0.5H);

MS (ESI+) 566 (M+H), 588 (M+23);

Anal. Calcd for C₂₃H₁₇NO₇SF₆: C, 48.85; H, 3.03; N, 2.47. Found: C, 48.96; H, 3.17; N, 2.45.

Example 192

[S-(R*,R*,R*)]-N-[1-(2,2,5-trimethyl-1,3-dioxol-4-yl)-2-[[4-(4-trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide

The title compound was prepared following the procedures described in example 145 except substituting commercially available methyl 3,4-isopropylidene-L-threonate for methyl (S)-2,2-dimethyl-1,3-dioxolane-4-carboxylate.

¹H NMR (300 MHz, DMSO-d₆) δ 1.2-1.3 (m, 9H), 3.3-3.5 (m, 2H), 3.6-3.9 (m, 3H), 4.1-4.2 (apparent t, 0.5H, J=5.0 Hz), 4.6-4.7 (apparent t, 0.5H, J=5.0 Hz), 7.2-7.3 (m, 4H),

7.48 (d, 2H, J=9.0 Hz), 7.85-8.00 (m, 2.5H), 8.15 (s, 0.5H), 9.69 (s, 0.5H), 9.95 (s, 0.5H); MS (ESI+) 520 (M+H), 537 (M+18);

Anal. Calcd for C₂₂H₂₄NO₈SF₃: C, 50.86; H, 4.65; N, 2.69. Found: C, 51.01; H, 4.38; N, 2.47.

Example 193

(⁺)-N-hydroxy-N-[1-(2-trifluoromethylphenyl)-2-[[4-(4-trifluoromethoxy)phenoxy]phenyl]sulfonyl]ethyl]formamide

The title compound was prepared according to the procedures of example 75,

except substituting 2-trifluoromethylbenzaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in example 75A.

¹H NMR (DMSO-d₆) δ 9.8 (bs, 0.5H), 8.17 (s, 0.5H), 8.10 (s, 0.5H), 7.5-7.98 (mm, 8H), 7.15-7.35 (mm, 4H), 6.05-6.15 (m, 0.5H), 5.48-5.50 (m, 0.5H), 4.39-4.44 (m, 1.0H), 3.90-4.15 (m, 2H);

MS (ESI) 550 (M+H), 567 (M+NH₄), 548 (M-H);

- 5 Anal. Calcd for: C₂₃H₁₇NO₆SF₆•0.25EtOAc; C, 50.44; H, 3.35; N, 2.454. Found: C, 50.50; H, 3.48; N, 2.32.

Example 194

(⁺)-N-hydroxy-N-[1-(4-fluorophenyl)-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]formamide

10

The title compound was prepared according to the procedures of example 75, except substituting 4-fluorobenzaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in example 75A.

15

¹H NMR (DMSO-d₆) δ 9.65 (s, 0.5H), 8.11-8.20 (m, 1H), 7.81-7.89 (d, 2H, 7.9Hz), 7.46-7.51 (d, 8.0H), 7.40-7.50 (m, 1H), 7.24-7.30 (d, 2H, 7.8Hz), 7.11-7.19 (d, 4H, J=8.0 Hz), 5.70-5.73 (bs, 0.5H), 5.48-5.51 (bs, 0.5H), 3.98-4.10 (m, 2H);

MS (ESI) 498 (M-H), 500 (M+H), 517 (M+NH₄);

Anal. Calcd for: C₂₂H₁₇NO₆SF₄; C, 52.90; H, 3.43; N, 2.80. Found: C, 52.63; H, 3.60;

20

N, 2.59.

Example 195

(⁺)-N-hydroxy-N-[1-(cyclohexyl)-2-[[4-(4-(trifluoromethoxy)phenoxy]phenyl)sulfonyl]ethyl]formamide

25

The title compound was prepared according to the procedures of example 75, except substituting cyclohexane carboxaldehyde for propionaldehyde and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-methoxyphenyl)phenyl methyl sulfone in example 75A.

30

¹H NMR (DMSO-d₆) δ 9.86 (s, 0.5H), 9.50 (s, 0.5H), 8.13 (s, 0.5H), 7.89-7.97 (m, 2H), 7.75 (s, 0.5H), 7.47-7.51 (d, 2H, J=7.8 Hz), 7.26-7.48 (m, 4H), 4.21-4.26 (m, 0.5H), 4.01-3.97 (m, 0.5H), 3.56-3.41 (m, 4H), 0.56-1.7 (m, 11H);

MS (ESI) 486 (M-H), 488 (M+H), 505 (M+NH₄);

Anal. Calcd for: C₂₂H₂₄NO₆SF₃•0.25H₂O; C, 53.70; H, 5.01; N, 2.84. Found: C, 54.67;

35

H, 5.35; N, 2.69.

Example 196

(-)(S) N-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

5

Example 196A

(S)-4-[[4-[(4-chlorophenoxy)phenyl]thio]methyl]-2-oxazolidinone

10

A 0° C solution of 4-(4'-chlorophenoxy)-benzenethiol (25.5g, 108 mmol) in DMF (250 mL) was treated with K₂CO₃ (14.9g, 108 mmol) followed by (S)-(+)-4-(4'-toluenesulfonyloxymethyl)-2-oxazolidinone (22.09 g, 83 mmol) [*J. Chem. Soc. Perkin Trans. 1. 1994, 13, 1675*]. The reaction was allowed to stir overnight at ambient temperature, then partitioned between ethyl acetate and brine. The organics were washed with brine twice, dried, filtered, concentrated and purified via silica gel chromatography eluting with 5 to 20 % ethyl acetate/hexane to give 22.08 g (81% yield) of the title compound.
MS (ESI) m/e 353 (M+NH₄)⁺.

15

20

Example 196B

(S)-4-[[4-[(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-oxazolidinone

A 0 °C mixture of 196A (3.6 g, 10 mmol) and NaHCO₃ (2.26 g, 26 mmol) in 200 mL of methanol and 50 mL of water was treated with oxone (9.6g, 27 mol), then stirred at room temperature for 3h, after which time the reaction was quenched with water and extracted with ethyl acetate. The organics were dried, filtered, and concentrated to give 3.53 g (96%) of the title compound.
MS (ESI) m/e 368 (M+H)⁺, 385 (M+NH₄)⁺, 390 (M+Na)⁺.

25

30

Example 196C

(S)-2-amino-3-[4-[(4-chlorophenoxy)phenyl]sulfonyl]-1-propanol

A mixture of 196B (3.53 g, 9.6 mmol) and NaOH (0.62 g, 15 mmol) in ethanol (20 mL) was stirred at reflux for 30h, then concentrated and partitioned between brine and CH₂Cl₂. The aqueous layer was back extracted with CH₂Cl₂ twice and the combined organics were washed with brine, dried, filtered, and concentrated to give 3.0 g (92%) of the title compound.

35

MS (ESI) m/e 342 (M+H)⁺, 364 (M+Na)⁺.

Example 196D

(-)(S)-N-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]hydroxylamine

A solution of 196C (9.89 g, 29 mmol) and 4-methoxybenzaldehyde (3.53 g, 29 mmol) in toluene (300 mL) was refluxed for 18h in a Dean-Stark apparatus. The reaction was then concentrated and the crude product was dissolved in THF (200 mL), sequentially treated with triphenyl phosphine (9.1 g, 35 mmol), 1,5,5-trimethyl hydantoin (4.9 g, 35 mmol) and diethyl azodicarboxylate (5.5 g, 35 mmol). The reaction was concentrated and the residue was dissolved in chloroform (100 mL), cooled to 0 °C, treated with 69 mL of sat. aq. NaHCO₃, and benzyltriethylammonium chloride (0.726g, 3.18 mmol) followed by dropwise addition of a solution of *m*-chloroperbenzoic acid (11 g, 32 mmol, 50%-Aldrich) in 100 mL CH₂Cl₂. The reaction was stirred at 0 °C for 7h then partitioned between water and CH₂Cl₂. The organics were washed with aq. NaHSO₃, water, brine, dried, filtered, and concentrated. The crude product was dissolved in 200 mL of methanol, treated with hydroxylamine hydrochloride (4 g, 58 mmol) and stirred at room temperature for 3 days. The reaction was then concentrated and the residue was partitioned between sat. aq. NaHCO₃ and ethyl acetate. The organics were dried, filtered, concentrated and purified via silica gel chromatography eluting with 1 to 5% methanol/methylene chloride to give 1.29 g (9%) of the title compound.

MS (ESI) m/e 482 (M+H)⁺, 504 (M+Na)⁺.

Example 196E

(-)-N-[1-[[[4-(4-chlorophenoxy)phenyl]sulfonyl]methyl]-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-N-hydroxyformamide

Example 196E was converted to the title compound following the procedure of example 2F.

mp 111 °C;
[α]_D = -6.4° (c= 0.25).

Example 197

(±)-N-hydroxy-N-[1-[[[4-(trifluorophenoxy)phenyl]sulfonyl]methyl]-2-(3,4,5-trimethoxyphenyl)ethyl]formamide

The title compound was prepared according to the procedures of example 126, except substituting ethyl 3,4,5-trimethoxyphenoxyacetate (prepared from ethyl bromoacetate and 3,4,5-trimethoxyphenol as in example 174A) for ethyl methoxyacetate and 4-(4'-trifluoromethoxyphenoxy)phenyl methyl sulfone for 4-(4'-trifluoromethyl-

5 phenyl)phenyl methyl sulfone.

¹H NMR (DMSO-d₆) δ 3.53-3.62 (m, 4H), 3.65-3.77 (m, 7H), 3.92-4.0 (m, 1H), 4.02-4.15 (m, 1H), 4.35-4.46 (bs, 0.5H), 4.85-4.97 (bs, 0.5H), 6.16 (d, 2H, J=4 Hz), 7.16-7.30 (m, 4H), 7.47 (d, 2H, J=9 Hz), 7.91 (d, 2H, J=12 Hz), 7.96 (s, 0.5H), 8.21 (s, 0.5H), 9.68 (s, 0.5H), 10.08 (s, 0.5H);

10 MS (ESI-) 600 (M-H)⁻;

Anal. Calcd for: C₂₆H₂₆NO₁₀SF₃ C, 51.91; H, 4.35; N, 2.32. Found: C, 51.90; H, 4.41; N, 2.26.